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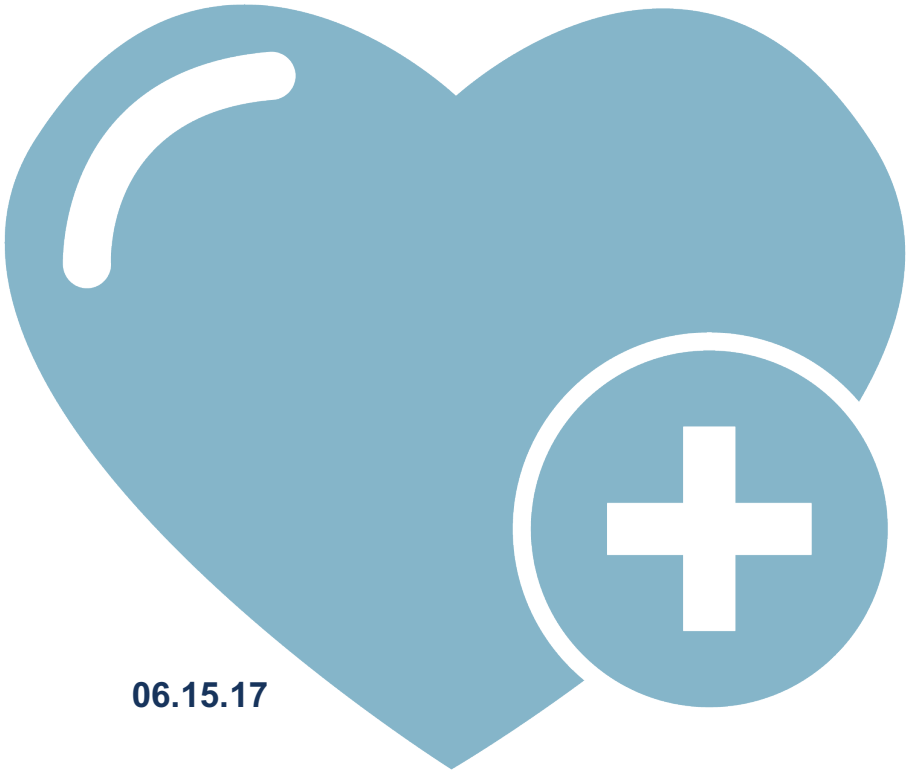
Grants Working Group Public Review Summary

Development of CLT030-ADC, a Leukemic Stem Cell Targeting Antibody-Drug-Conjugate, for Treatment of Acute Myeloid Leukemia

Application Number: CLIN1-09776 (Revised Application)	Review Date: 08 June 2017

Late Stage Preclinical Project Proposal (CLIN1)



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Development of CLT030-ADC, a Leukemic Stem Cell Targeting Antibody-Drug-Conjugate, for Treatment of Acute Myeloid Leukemia

APPLICATION NUMBER: CLIN1-09776 (Revised application)

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PROGRAM ANNOUNCEMENT: CLIN1 Late Stage Preclinical Projects

Therapeutic Candidate or Device

CLT030-ADC, a novel drug targeting a leukemic stem cell surface protein CLL1

Indication

Acute Myeloid Leukemia (AML) patients.

Therapeutic Mechanism

CLT030-ADC is an antibody-drug conjugate targeting leukemic stem cell surface protein CLL1. Leukemic stem cells (LSC) are believed to be responsible for disease recurrence and are resistant to chemotherapy. CLT030-ADC specifically targets LSC as a primary mode of action. CLT030-ADC is stable in the bloodstream and releases its DNA binding payload upon binding to LSC and internalization. The payload binds to the cellular DNA and kills the cell.

Unmet Medical Need

The current standard of care for AML patients is inadequate as evidenced by low survival rates. The chemotherapy does not kill LSC, which are believed to be responsible for relapse. By targeting LSC with CLT030-ADC, remission rates could be higher resulting in prolonged survival.

Project Objective

Filing of IND for Phase 1 trial.

Major Proposed Activities

Complete nonclinical and IND-enabling activities including GLP toxicity studies.

Manufacture product to support IND enabling activities and Phase 1 trial.

Generate clinical protocol and file IND for Phase 1 trial.

Funds Requested

$6,863,755 ($1,715,939 Co-funding)

Recommendation

Score: 1

Votes for Score 1 = 11 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

This is a revised application that previously received a score of "2". In the initial review of this application, the reviewers thought that targeting leukemic stem cells with an ADC could be a safe and effective treatment approach for AML patients. However, the reviewers had expressed several concerns including prevalence of CLL1 expression in AML patient samples, lack of evidence for the ADC's LSC targeting activity, off-target activity of the ADC on normal cells and inadequate information on the cytotoxic payload. In reviewing the revised submission reviewers thought that the applicant had provided adequate additional information and had included additional studies that will demonstrate LSC targeting activity and safety of the proposed treatment. Therefore, reviewers recommended the 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.

- AML is the most common leukemia in adults with high relapse and low survival rates. A safe and effective treatment for AML remains a significant unmet medical need.
- Leukemic stem cells (LSC) are believed to play a major role in the poor prognosis for AML and thus a treatment that targets these cells would address the 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 approach, if shown to effectively target LSC, could have potential to extend remission and provide an improvement over 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.

- CLL1 is expressed on LSC in a significant subset of AML patients. The targeted ADC treatment could be impactful for these patients.

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.

- CLL1 is a well-characterized LSC target in AML patients. The applicant provided additional FACS data showing CLL1 expression profile in samples from multiple patients as further support for targeting CLL1.
- The preclinical data presented to date demonstrated tumor debulking activity of the agent but did not demonstrate specific LSC targeting activity.
- CLL1 is expressed on normal hematopoietic progenitor cells and myeloid cells. These cells will need to be accounted for in any safety and efficacy studies performed on the candidate.
- There was minimal data provided on the cytotoxic payload in the original submission of this application. The applicant provided adequate technical information on the candidate in the revised submission.

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Public Review Summary

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

- Based on the additional data provided in the resubmission, the reviewers thought that the data supported continued development of the ADC candidate.

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.

- Successful outcome of the testing plan will enable IND filing. However, some reviewers thought that the applicant should conduct a Pre-IND meeting.
- Based on reviewer recommendations, LSC targeting activity will be studied in vivo using serial transplantation assays.
- Off-target activity on normal myeloid and hematopoietic progenitor cells will be studied in animal models.
- The applicant provided adequate rationale for using non-GMP material in GLP studies include awareness for demonstrating comparability.
- The preclinical studies will provide a thorough safety profile of the candidate.
- The applicants were responsive to reviewers concerns and recommendations in the revised submission.

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

- This is a well-constructed program.
- The applicant will rely on GLP and GMP vendors to support toxicology and CMC.

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.

- The objectives are likely to be achieved within the proposed timeline.

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 has the appropriate experience and qualifications and access to resources needed to complete the IND enabling activities.
- The team includes experienced consultants.
- The trial design should be informed by consultation with key opinion leaders experienced in developing ADC and in conducting oncology trials.

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

- The team identified relevant manufacturing risks and has a viable contingency plan to manage these risks.

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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).