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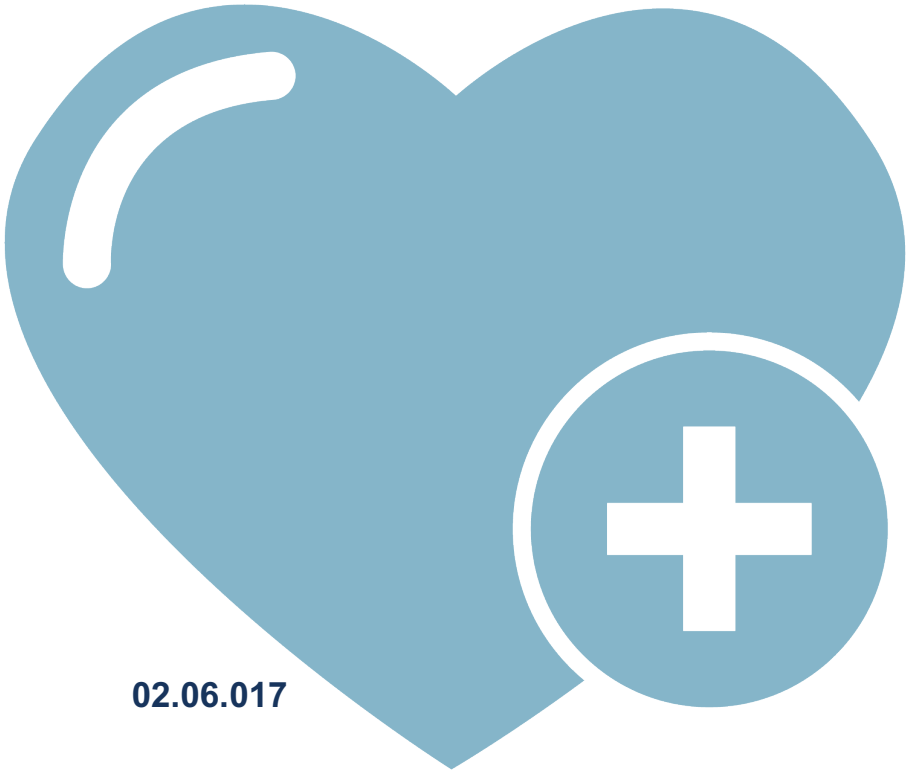
Grants Working Group Public Review Summary

Phase 2 Safety and Efficacy Study of CLBS03 Autologous T-Regulatory Cells in Adolescents with Recent Onset Type 1 Diabetes Mellitus

Application Number: CLIN2-09730 (Revised Application)	Review Date: 31 January 2017

Clinical Trial Stage Project Proposal (CLIN2)



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Phase 2 Safety and Efficacy Study of CLBS03 Autologous T-Regulatory Cells in Adolescents with Recent Onset Type 1 Diabetes Mellitus

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REVIEW DATE: 31 January 2017

PROGRAM ANNOUNCEMENT: CLIN2 Clinical Trial Stage Projects

Therapeutic Candidate or Device

Autologous Ex Vivo Expanded Polyclonal CD4+CD25+CD127lo/-FOXP3+ Regulatory T-cells (CLBS03)

Indication

Early Onset Type 1 Diabetes Mellitus (T1D) with Residual Beta Cell Function

Therapeutic Mechanism

The mechanism(s) by which the immune system become unrestrained, resulting in the destruction of pancreatic beta-islet cells, is not known. Evidence indicates that regulatory T-cells (T-regs) maintain immune balance at least in part by control of differentiation of multipotent progenitor/stem cells.

Unmet Medical Need

No therapy that maintains or restores pancreatic beta islet cell function is currently approved. Children with T1D face lifelong struggles with glycemic control and, despite careful management, an increased risk of severe complications.

Project Objective

Phase 2 trial completed

Major Proposed Activities

Enrollment and treatment of the remaining 92 subjects in the phase 2 clinical trial

Manufacturing investigational product for the remaining subjects in the trial

Funds Requested

$12,211,255 ($8,140,837 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

Reviewers unanimously agreed that the proposed project should be recommended for funding. The proposed therapeutic holds the potential to improve the standard of care and clinical outcomes in a disease that represents a huge individual and healthcare burden. Further, the project is based on strong preclinical and clinical rationale, the team is outstanding, and the clinical trial is extremely well designed.

Review Summary

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

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

- Type 1 Diabetes Mellitus (T1D) represents a clear unmet medical need as most patients with this disease are unable to achieve glycemic control with currently available treatments.
- T1D represents a significant public health problem with huge burden on the individual and medical system.
- The proposed treatment holds promise to fulfill this unmet medical need.

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

- This treatment holds the potential to provide insulin independence, which would be a huge improvement to the standard of care even if repeat administration of the treatment is required.
- If the treatment does not provide insulin independence but maintains residual c-peptide secretion, quality of life, morbidity, and mortality would be improved by this treatment as compared to the current standard of care.

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

- The value proposition is difficult to assess at this stage, where cost is unknown. However, there is potential with this treatment that the clinical benefit could be large, so if successfully developed, the value proposition to patients and health care providers would be sufficient, impactful, and practical regardless of cost.

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.

- The scientific rationale supporting this project is strong.
- In the first review of the application, reviewers were concerned that some of the existing Phase 1 data was not as expected. However, the applicant's response to reviewer concerns allayed these concerns. Reviewers noted that the applicant is appropriately evaluating the clinical data set; that the current clinical data supports use in the target patient population; and that the clinical rationale for the proposed project is strong.
- Current clinical data supports a favorable safety profile for the treatment.
- During the first review of this application, reviewers were concerned that the product may switch phenotypes *in vivo* and not act as predicted to modify

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disease. However, the applicant addressed this concern to reviewers' satisfaction.

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

- Current clinical data strongly supports the continued development of the therapeutic 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.

- Reviewers were impressed with the design of the clinical trial and noted that it is one of the best trial designs they have evaluated.
- During the first review of this application, reviewers were concerned that the endpoint strategy may not include an approvable endpoint. This concern was allayed in the revised application as FDA communications indicated that indicated the proposed endpoint strategy would be acceptable for registration.
- Reviewers expressed some concerns with product release criteria during the first review of this application. The applicant adequately addressed these concerns, and reviewers are comfortable with the quality and consistency of the product and with its release criteria.
- At the first review of this application, reviewers suggested that the applicant add continuous glucose monitoring (CGM) to the trial. The applicant added this study to the clinical protocol, but reviewers recommended the applicant reconsider certain aspects of the plan to ensure uniformity. A standard device and protocol for its use should be implemented.

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

- The program is well-constructed and of high quality.

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

- The timelines and project plan demonstrate and urgency commensurate with CIRM's mission.

Is the project feasible?

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

- The timelines are feasible and objectives likely to be achieved as proposed.

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 outstanding and appropriate to carry out the proposed work.
- The team has access to all necessary resources to conduct the proposed activities.
- The partnerships are appropriate and improve the likelihood of success.

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

- The contingency plan is adequate, and reviewers did not have any concerns regarding management of risks and delays.

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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).