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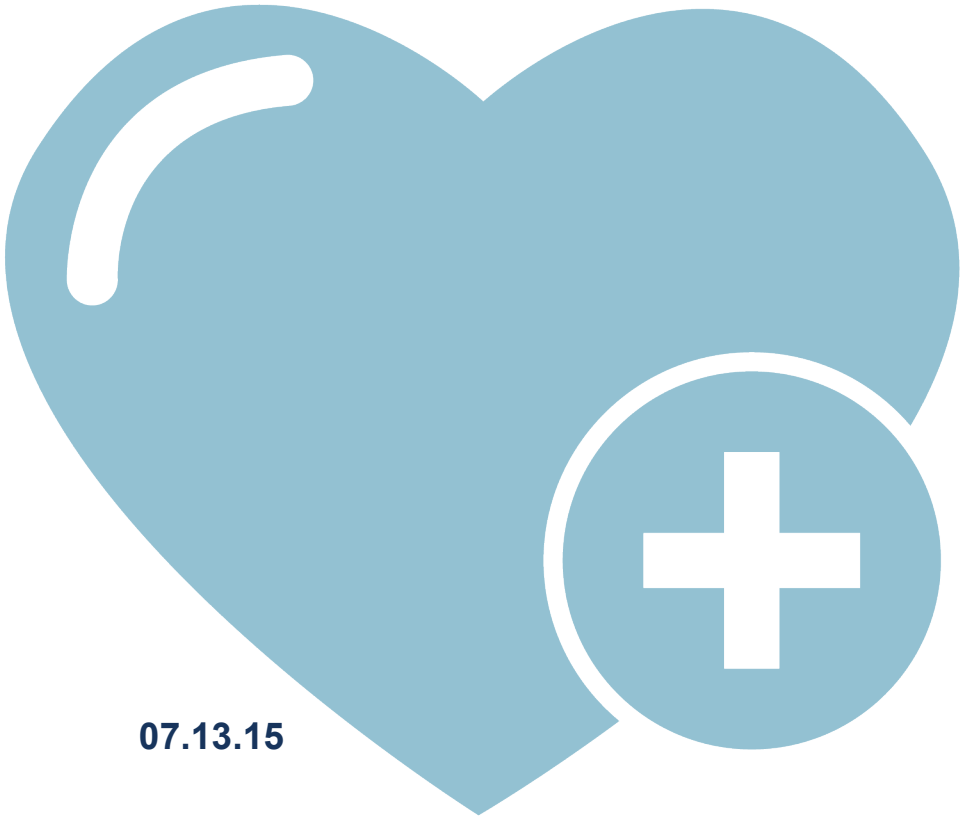
Grants Working Group Public Review Summary

A Phase I/II, Non Randomized, Multicenter, Open-Label Study of G1XCGD (Lentiviral Vector Transduced CD34+ Cells) in Patients With X-Linked Chronic Granulomatous Disease

Application Number: CTS1-08231 #2	Review Number: CP2015 June Revisions

Clinical Trial Stage Project Proposal



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A Phase I/II, Non Randomized, Multicenter, Open-Label Study of G1XCGD (Lentiviral Vector Transduced CD34+ Cells) in Patients With X-Linked Chronic Granulomatous Disease

APPLICATION NUMBER: CTS1-08231 #2

REVIEW NUMBER: CP2015 June Revisions

PROGRAM ANNOUNCEMENT: Clinical Trial Stage Projects

Therapeutic Candidate

Autologous CD34+ hematopoietic stem/progenitor cells (HSPC) transduced with the G1XCGD lentiviral vector

Indication

Patients with severe X-linked Chronic Granulomatous Disease (XCGD) lacking matched donors

Unmet Medical Need

Hematopoietic stem cell transplantation (HSCT) from non-fully matched donors may have immune complications and requires potent immune suppression. Effective autologous HSCT with G1XCGD lentiviral vector-mediated gene correction could have similar benefits but be safer with fewer complications.

Major Proposed Activities

GMP manufacture of patient-specific lots of G1XCGD transduced autologous CD34+ HSPC meeting release criteria.

Transplant subjects with severe XCGD lacking matched donors with the autologous stem cell product after reduced intensity conditioning (conduct a clinical trial).

Perform two-year follow up to assess trial end-points to assess safety and efficacy.

Funds Requested

$7,402,549 ($4,633,848 Co-funding)

Recommendation

Score: 1

Votes for Score 1 = 5 GWG members

Votes for Score 2 = 1 GWG members

Votes for Score 3 = 4 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.

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Review Overview

Reviewers agreed that this is a high quality project proposed by an outstanding team, and that the therapeutic has the potential to address a serious unmet medical need. Reviewers were, however, divided as to the feasibility. Some reviewers did not think that there are sufficient patients afflicted with this disease who also meet the enrollment criteria to allow for completion of the trial with enough patients to yield meaningful outcomes. Other reviewers were optimistic that, given the track record of this team and the willingness of patients with intractable orphan diseases to participate clinical trials, the trial could be fully enrolled and yield results to potentially support moving the therapeutic toward approval by the FDA and/or advance the field.

Review Summary

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

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

- XCGD represents an unmet medical need. Patients are currently treated with either antibiotics or bone marrow transplant, neither of which is satisfactory. This therapy, if successfully developed, could offer an effective alternative.
- Reviewers noted that this is an orphan disease with an extremely small number of patients, therefore, the therapy could provide benefit, but the number of patients impacted will be small.

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

- Reviewers thought the proposed approach could provide an improvement to the standard of care for patients with XCGD.

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

- Without knowing the cost, durability, or effectiveness of the therapy, any projection of value or cost savings is speculative. However, this therapy does have potential to provide value to both patients and providers.
- If the therapy proves effective and is licensed with the FDA, it could help establish proof of concept for the approach, which would be an important step forward in the field and have potential value in a number of other diseases.

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.

- Although logistically complex, the proposed therapy replaces a single gene and includes a discrete way to measure efficacy via a well-established assay.
- Reviewers would have liked additional data supporting the adequacy of the observed transduction efficiency and the proposed conditioning regimen to achieve engraftment of corrected cells at a level that produces a biologic effect and provides benefit. However, conduct of the proposed trial may be the best way to provide this supporting data.

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

- The data supports safety, efficacy, and continued development of the

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proposed therapeutic.

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 achieves meaningful outcomes to support further development of the therapeutic candidate.

- The project is meticulously planned and organized and is designed to achieve meaningful outcomes, including determination of the toxicity profile, treatment plan, and reconstitution potential of the corrected cell population.
- Reviewers expressed minor concerns regarding development of a potency assay, but thought this could be addressed later in development.

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

- The program is well thought out, appropriately designed, and of high quality.

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

- The project plan does demonstrate an urgency commensurate with CIRM's mission, but the low prevalence of the disease raises concerns as to whether or not the plan is executable.

Is the project feasible?

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

- Some reviewers thought the proposed number of patients would be the minimum number required to get meaningful results and expressed concern as to the feasibility of recruiting and enrolling that number of patients, given the rarity of patients who meet the enrollment criteria. This was thought to be a potentially unsolvable issue.
- Some reviewers acknowledged that enrollment would be challenging but were optimistic regarding the feasibility of meeting enrollment projections given the track record of the team and the historical willingness of patients with intractable orphan diseases to participate in these types of trials.

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 has access to all necessary resources to conduct the proposed activities.
- The team has a track record of success in conducting clinical trials with similar challenges.

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

- The team provided a viable contingency plan to manage risks such as graft failure and immune recognition of the gene product.
- Some reviewers thought the primary risk, which is a failure to enroll the trial due to a paucity of patients, could not be addressed by a contingency plan.

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CIRM Recommendation

The CIRM team met after the GWG to consider its recommendation to the Application Review Subcommittee. This section will be posted publicly.

RECOMMENDATION: Fund (CIRM concurs with the GWG recommendation)

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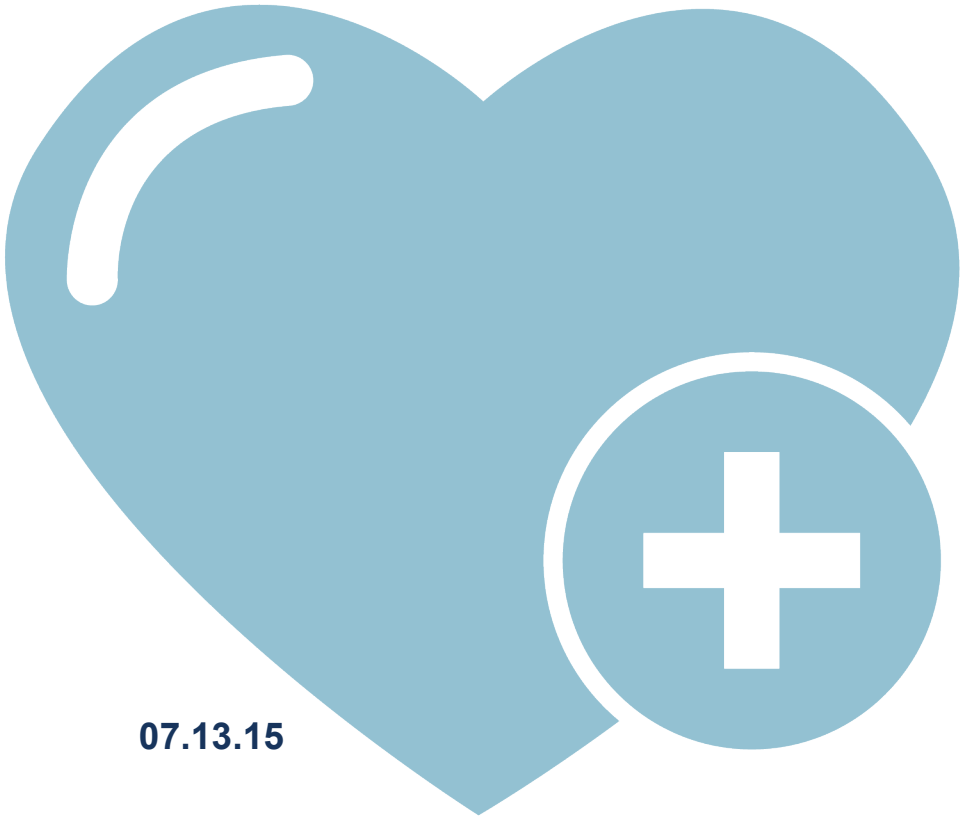
Grants Working Group Public Review Summary

Stem Cell Gene Therapy for HIV Mediated by Lentivector Transduced, Pre-selected CD34+ Cells in AIDS Lymphoma Patients

Application Number: CTS1-08289 #2	Review Number: CP2015 June Revisions

Clinical Trial Stage Project Proposal



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Stem Cell Gene Therapy for HIV Mediated by Lentivector Transduced, Pre-selected CD34+ Cells in AIDS Lymphoma Patients

APPLICATION NUMBER: CTS1-08289 #2

REVIEW NUMBER: CP2015 June Revisions

PROGRAM ANNOUNCEMENT: Clinical Trial Stage Projects

Therapeutic Candidate

Hematopoietic stem cells (HSC) gene-modified by a lentiviral vector, which encodes a triple combination of HIV-resistance genes and a pre-selective marker.

Indication

HIV in AIDS-lymphoma patients

Unmet Medical Need

HIV continues to be a public health problem worldwide with no effective vaccine or cure available. Despite anti-retroviral therapy prolonging lives of patients, it is not curative. HIV stem cell gene therapy provides the potential to replace a patient's immune system with one resistant to HIV.

Major Proposed Activities

Manufacture GMP grade anti-HIV lentivector and clinical grade HIV-resistant HSC.

Conduct a Phase I study of safety, feasibility, and efficacy of our product in AIDS-lymphoma patients.

Evaluate the correlatives of transplanted cells including DNA, immune, and virologic monitoring.

Funds Requested

$8,521,441 ($0 Co-funding)

Recommendation

Score: 1

Votes for Score 1 = 10 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.

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Review Overview

Reviewers considered this to be an impactful, well designed, and feasible project. There were minor concerns regarding the difficulty of manufacturing the final product, but overall, reviewers found the applicant to be responsive to reviewer suggestions and thought results from this trial could potentially advance development of curative therapies for HIV positive patients.

Review Summary

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

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

- Improvement of treatment options for HIV positive individuals is an important unmet medical need. It is not clear whether this therapeutic approach (use of gene-modified HSC) will ultimately impact this need, but the proposed therapy provides a suitable and important attempt.

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

- If successful engraftment of sufficient HIV-resistant precursors ultimately leads to improved immune functionality, this would be a significant improvement over standard of care in the proposed AIDS lymphoma patient population.
- Some reviewers considered it unlikely that the therapy as proposed will result in an improvement over standard of care for (non-lymphoma) HIV positive patients, but thought this trial to be a key step toward a curative therapy.

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

- With the proposed patient population (AIDS lymphoma patients), impact will be somewhat limited. However, demonstration of success in this limited context would serve as an impetus to solve additional problems such as non-ablative conditioning to achieve engraftment in the larger HIV patient population.
- In the proposed patient population, the proposed trial is reasonable with the potential for impact.

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 strong scientific rationale includes reasonable and extensive preclinical data supporting all components of this approach.
- In order to provide confidence that there will be sufficient engraftment of transduced cells to confer benefit to patients, reviewers would have appreciated additional data supporting an *in vivo* selective advantage to transduced cells, but recognized this data may need to come through the conduct of the trial.
- Reviewers thought the rationale for how this approach could eradicate HIV reservoirs was weak and in need of additional consideration.

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

- Continued development is supported by the extensive preclinical data.

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- With the current manufacturing process and patient population, reviewers were not convinced that a sufficient number of cells can be collected from an individual patient to consistently generate the minimum number of cells necessary for transplantation of the final product. This is both a safety and feasibility concern, but one that is addressable and did not significantly impact enthusiasm for 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 achieves meaningful outcomes to support further development of the therapeutic candidate.

- Reviewers thought the trial to be well designed to support meaningful outcomes, including establishing initial safety of the proposed product and providing data to rapidly advance the field.
- Reviewers expressed some safety concerns with the original trial design, particularly related to the proposed antiretroviral drug treatment interruptions and proposed endoscopy procedures, but the applicant agreed to modifications that allayed these concerns.

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

- The program is of high quality and is proposed to be conducted at a high quality facility.

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

- The timeline is appropriately extended to ensure sufficient safety follow-up between cohorts and to accommodate enrollment challenges and demonstrates an 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.

- There are enrollment challenges, but reviewers thought the team capable of managing and addressing the challenges.
- The timeline is appropriate to allow for achievement of the objectives within the 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 is excellent and has access to all necessary resources.
- The investigator is highly qualified and able to lead the proposed activities.

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

- The applicant presented a well defined contingency plan to manage risks.
- The applicant should identify supply chain risks, especially where reliant on a sole-source reagent.

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CIRM Recommendation

The CIRM team met after the GWG to consider its recommendation to the Application Review Subcommittee. This section will be posted publicly.

RECOMMENDATION: Fund (CIRM concurs with the GWG recommendation)