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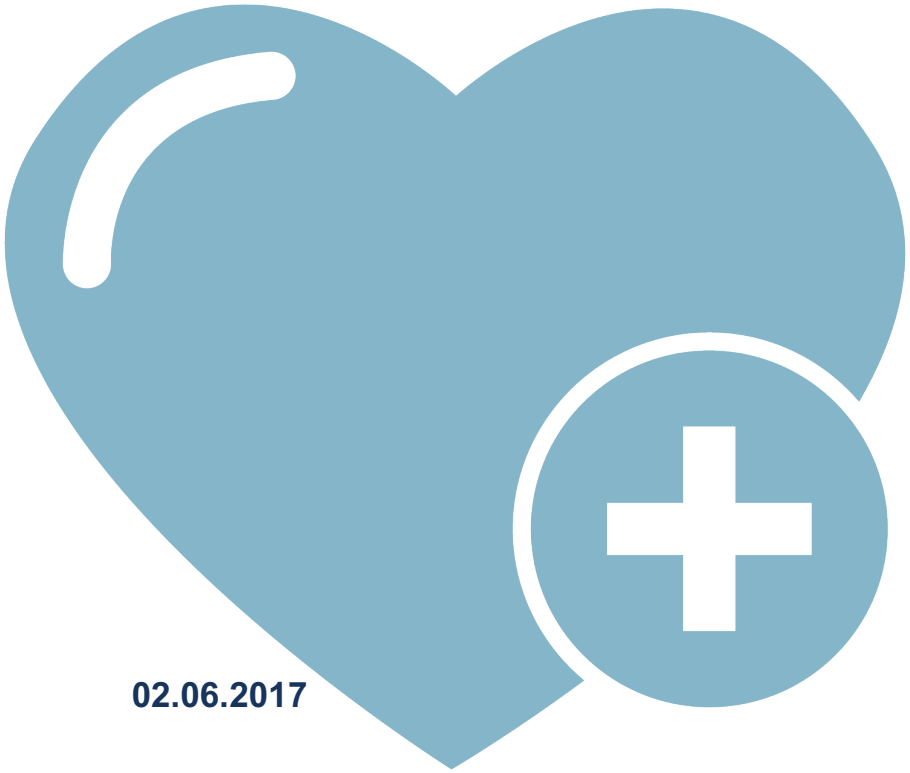
Grants Working Group Public Review Summary

Human Neural Progenitors Secreting Glial Cell Line-Derived Neurotrophic Factor (CNS10-NPC-GDNF) for the Treatment of Amyotrophic Lateral Sclerosis

Application Number: CLIN2-09284 (Revised Application)	Review Date: 31 January 2017

Clinical Trial Stage Project Proposal (CLIN2)



02.06.2017

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Human Neural Progenitors Secreting Glial Cell Line-Derived Neurotrophic Factor (CNS10-NPC-GDNF) for the Treatment of Amyotrophic Lateral Sclerosis

APPLICATION NUMBER: CLIN2-09284 (Revised application)

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PROGRAM ANNOUNCEMENT: CLIN2 Clinical Trial Stage Projects

Therapeutic Candidate or Device

CNS10-NPC-GDNF - a neural progenitor cell secreting GDNF

Indication

Amyotrophic Lateral Sclerosis (ALS)

Therapeutic Mechanism

This therapy will replace damaged astrocytes. The new astrocytes will release paracrine factors. As the cells have been modified to release GDNF they will also provide this factor to dying motor neurons.

Unmet Medical Need

There is no treatment or cure for ALS. Thus there is a huge unmet medical need.

Project Objective

Phase 1/2a clinical trial

Major Proposed Activities

Assess clinical safety of the therapeutic product

Funds Requested

$6,154,067 ($0 Co-funding)

Recommendation

Score: 1

Votes for Score 1 = 7 GWG members

Votes for Score 2 = 3 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 agreed that this project targets a tremendous unmet medical need; is led by an excellent and dedicated team; and proposes an innovative and well thought out clinical trial. Some reviewers were concerned that the preclinical data does not adequately support a likelihood of clinical benefit. However, the majority of reviewers thought the preclinical data package was strong and supports initiation of clinical testing in humans with this therapeutic candidate. Therefore, this project is recommended 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.

- ALS is a relentlessly progressive and universally fatal disease for which there are poor treatment options. The proposed treatment holds the potential to provide an improved treatment option for this patient population.

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

- ALS is a diffuse disease, and the proposed treatment is necessarily focal. However, there are currently limited therapeutic treatment options available for these patients, and this treatment holds potential to both improve the quality of life and slow disease progression.

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

- A treatment that could improve the quality of life or slow disease progression would offer a sufficient, impactful, and practical value proposition for patients and health care 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.

- The scientific rationale is strong, and GDNF is a good, validated target in this disease.
- Reviewers agreed the safety data supports initiation of clinical testing in humans.
- In the first review of this application, reviewers requested access to additional data to ascertain whether the proposed product has the necessary biologic activity to exert the proposed effects. In the resubmitted application, the applicants provided all requested data. Reviewers thought the biologic data to be strong and that it supported initiation of clinical testing in humans.
- Reviewers noted that the preclinical data does not provide evidence of a clinical benefit or demonstrate a disease-modifying effect.
    - Some reviewers noted that the animal models of ALS are not reflective of human disease and found little predictive value in testing for clinical benefit or disease-modifying activity in these animal models. These reviewers thought that the biologic data is a better

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indicator of potential clinical benefit; that demonstration of clinical benefit can only be achieved through clinical testing in humans; and that the body of data supports conduct of the proposed clinical study.

- Other reviewers thought that additional preclinical animal model data that provides some evidence that clinical benefit is likely or of disease-modifying activity is needed before initiating the proposed clinical study.

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

- While all reviewers agreed that the data supports continued development of the therapeutic candidate, some reviewers would like to see additional data before initiating clinical development. Other reviewers thought the safety, biologic, and mechanistic preclinical data indicate that the project is ready to initiate clinical testing.

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.

- The proposed clinical protocol is well designed to assess initial safety and exploratory efficacy endpoints.
- The trial design is supported by extensive natural history patient data and is also innovative due to an interesting approach that has been developed by the investigator to measure a potential efficacy signal.
- Some reviewers noted that changes to the protocol suggested by reviewers during the first review of this application were not adopted by the applicant in the resubmitted application.

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

- Reviewers agreed this is a well-constructed, quality program.
- Reviewers noted that the applicant has developed a cell delivery device that supports the project and can be used for other applications.

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

- The project plan and timeline demonstrate an urgency that is commensurate with CIRM's mission.
- In the first review of this application, reviewers were concerned that the overall clinical development plan lacked urgency to move forward to clinical testing in the cervical spine region, where clinical benefit is most likely. However, the applicant provided a rationale as to how the proposed plan is likely to lead to a stronger data package, and reviewers were comfortable with the arguments presented.

Is the project feasible?

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

- The intended objectives are likely to be achieved within the proposed timelines.
- Reviewers noted that the team has gained valuable experience from the

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translational and preclinical work already conducted, and reviewers are confident they are can carry out the proposed work.

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 first-class and has shown dedication and persistence in bringing this product to clinical testing.
- The team has the necessary resources to conduct the proposed activities.
- The team includes respected members of the ALS community, which strengthens the proposal.

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

- Potential risks are clearly identified as are viable mitigation strategies.

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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).