Application #	CLIN2-12319
Title (as written by the applicant)	Neural progenitor cells delivered into the motor cortex for the treatment of ALS
Therapeutic Candidate (as written by the applicant)	A neural progenitor cell secreting GDNF
Indication (as written by the applicant)	Amyotrophic Lateral Sclerosis (ALS)
Unmet Medical Need (as written by the applicant)	There are currently only two FDA-approved therapies with minimal benefits, but there is no cure for ALS. Thus, there is a huge unmet medical need to find additional therapies with longer-lasting benefits.
Major Proposed Activities (as written by the applicant)	• Enrollment of 16 patients to a Phase 1/2a trial to demonstrate safety and preliminary efficacy of the cellular product • GMP manufacturing of a new product working cell lot for future clinical trials in ALS.
Funds Requested	$11,990,372
GWG Recommendation	Tier 1: warrants funding

SCORING DATA

Final Score: 1

Up to 15 scientific members of the GWG score each application. The final score for an application is the average of the individual member scores. Additional parameters related to the score are shown below.

Highest	1
Lowest	2
Count	13
Votes for Tier 1	10
Votes for Tier 2	3
Votes for Tier 3	0

- 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.

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 13	• ALS is a disease of huge unmet need. • Yes - this proposal aims to use neural progenitor cells which have been engineered to express GDNF to slow progression of ALS. The thesis is that these cells will differentiate into astrocytes, remain viable and secrete GDNF locally. The data support this thesis. • Given the ghastly nature of ALS I believe this initiative is well worth supporting. While this approach is unlikely to be curative, if there is any slowing of progression of ALS it would be a very significant result. • Exciting approach backed by a large body of previous data, however, only modest effects from previous clinical trials. Changes made to the protocol may improve results. • There is potential to definitively test the hypothesis related to the role of GDNF in this disease. • Huge unmet need and strong team.
No: 0	*none*
GWG Votes	Is the rationale sound?
Yes: 13	• Pre-clinical data supports the hypothesis. Systemic delivery of GDNF does not deliver this growth factor to crucial sites in the central nervous system so this approach aims to circumvent that

	problem by implanting cells that will survive and make GDNF at crucial sites in the central nervous system. ● Supported by preclinical data. ● The functional clinical data for the cell transplant in the lumbar spine are not compelling for any signal to efficacy and the lower dose was statistically better than the higher dose. ● The pre-clinical data for the upper motor neurons are supportive in terms of GDNF production and the large animal model are reassuring about the lack of neuroma formation (although this did not examine function as was an engraftment rather than disease model). ● I would like to see a statistical analysis plan based on the observed effect size seen in the lumbar clinical trial. I recognize that the effect size could be larger with the cortical injection, but it's worthwhile to see what the Phase 2/3 clinical trial size needs to be.
No: 0	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 12	● Well-designed study maximizing data collection. ● This is a great team, and the study is well planned and supported by a lot of pre-clinical data. ● The comment on the planned myeloablative regimen being worked out by the pharmacist seems poorly thought out. ● The study is well designed overall but statistical justification is not adequate. The clinical trial is predominantly based on safety/tolerability, but the information on how they would have 80% power to see a 66% change and at what time point, or in the other secondary outcome efficacy measures is not presented. It is critical to understand there is power to detect clinical differences, which was not convincingly shown in the lumbar spine studies, so that the next phase trial can be adequately designed. What would the thresholds for improvement in any of those given measures be to allow progress to the next phase? ● Clarify whether a DSMB will be used in study. Consider a power calculation on efficacy. ● The suggestions from the reviewers for additional work seem relatively minor and readily accomplished.
No: 1	● Please provide power analysis.
GWG Votes	Is the proposal feasible?
Yes: 13	● Feasible with an excellent team. ● Yes, I have no doubt this team will be able to execute on the plan. ● Need to understand rate of enrollment from the lumbar study. Can they replicate it for the cerebral? ● I am not sure that the low vs high dose efficacy signal is reflected in their planned dosing regimens. ● I am not sure about the rationale for funding additional cell funding without evidence of efficacy.
No: 0	*none*
GWG Votes	Does the project serve the needs of underserved communities?
Yes: 13	● Given the small number of trial subjects planned, diversity in the patient population is a challenge. They have documents in multiple languages and translators available. They should reduce those barriers. They have experience with the ALS population and to their credit report what they think are truly realistic numbers, not hypothetical. They have contingency plans that can extend their reach geographically if needed.
No: 0	*none*

DIVERSITY, EQUITY, AND INCLUSION IN RESEARCH

Following the panel's discussion of the application, the patient advocate members of the GWG were asked to indicate whether the application addressed diversity, equity and inclusion, and to provide brief comments. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

DEI Score: 8

Up to 7 patient advocate members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Score	Patient Advocate Votes	Has the applicant sufficiently addressed how they have or will incorporate perspectives from individuals with diverse experience and from underserved groups in the implementation of the proposed project?
9-10: Outstanding response		*none*
6-8: Responsive	1	• Indication (ALS) is a 100% lethal neurodegenerative disease with no effective therapy. This is a major unmet medical need. • The institution is committed to Institution-wide promotion of diversity as demonstrated by programs, policies, education, training - a serious financial investment. • The research team is quite diverse including members in positions of power and influence, including the PI.
3-5: Not fully responsive		*none*
0-2: Not responsive		*none*