Application #	CLIN2-13162 #2
Title (as written by the applicant)	A Phase I Study of Multiple doses of Neural Stem Cell (NSC)-Based Oncolytic Virotherapy Administered Intracerebrally to Patients with Recurrent High-Grade Gliomas
Therapeutic Candidate (as written by the applicant)	Neural stem cells (NSCs) that are genetically engineered to express a cancer-killing virus that specifically targets brain tumor cells
Indication (as written by the applicant)	Recurrent brain tumors in adults: high grade gliomas (HGG) such as glioblastoma (GBM)
Unmet Medical Need (as written by the applicant)	GBM (a type of HGG) is the most common malignant adult primary brain tumor. GBM is an aggressive cancer, and survival of GBM patients is typically less than two years after diagnosis despite current therapies. Thus, there is an urgent need for new therapies to improve survival of GBM patients.
Major Proposed Activities (as written by the applicant)	• Manufacture cGMP clinical lots of the therapeutic agent to supply the proposed clinical trial. • Complete a phase I clinical trial to determine safety and the recommended number of weekly doses of the therapeutic agent. • Determine biologic activity, biodistribution, immunogenicity, and preliminary clinical efficacy.
Funds Requested	$11,999,984
GWG Recommendation	Tier 1: warrants funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

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	15
Votes for Tier 1	11
Votes for Tier 2	4
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/RFA. 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: 15	• Recurrent glioblastoma multiforme (GBM) has significant unmet need. However, it's unclear how this approach will overcome immunosuppression and heterogeneity. • The efficacy data from preclinical studies is tepid and the models used are not prototypical GBMs - GL261 is very immunogenic and responsive to immunotherapy, and U87 is not GBM. I would encourage repeat testing in more physiologically relevant systems. • Yes, GBM is a common and highly aggressive glioma in adults. There are very limited impactful treatment options for GBM and there is a significant need for new therapies. • As indicated in the proposal, although nearly all GBM patients develop tumor progression after first-line therapy there appears to be no second-line treatment or standard of care for recurrent GBM. Mean overall survival is approximately 9 months. • As GBM is currently an incurable clinical indication, an improvement in progression free survival (PFS) or overall survival (OS) would provide a strong case for adoption. • This is a major area of unmet need. Tumor type is potentially addressable with an intratumoral approach. • It is unclear based on prior similar (Phase 1) trials if this treatment paradigm can be a successful modality in the management of glioblastoma. Previous studies have been performed in recurrent and newly diagnosed malignant glioma.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 14	• The applicants have generated a robust pre-clinical data set that supports the overall rationale and justification to proceed to a clinical trial. • Among other things, the applicants demonstrate the therapeutic advantage of their therapy in terms of distribution in an orthotopic glioma model. They have also shown that multiple administrations of the therapy prolong survival of mice bearing glioma orthografts. • Furthermore, the applicants show that neural stem cells (NSCs) can protect the expressed gliomatropic oncolytic adenovirus from complement-mediated destruction and neutralizing antibodies, indicating it may be feasible to administer the therapeutic in repeat doses. • Sound scientific data and clinical rationale have been provided. These include compelling nonclinical study data and promising prior clinical experience in GBM patients. • Single dose administration of the proposed product demonstrated initial safety in a previous human clinical study. This result supports continued clinical development of this treatment using multiple doses. • The rationale is sound. Strong correlates are built into the trial design to monitor participant response. However, I would recommend adding prospective pharmacodynamic endpoints (informed by preclinical studies) to the trial design to ensure the agent is biologically active. • Given the unmet need the rationale for the project is sound on scientific and clinical rationales. • The applicant provides appropriate responses to prior critiques.
No: 1	• Previous work in newly diagnosed glioma (single dose) revealed viral meningitis after inadvertent injection of NSC-virus into the lateral ventricle. In the current trial, it is not clear how viral injection into the resection cavity (which is in continuity with subarachnoid space) and via a Rickham catheter can be prevented from entering the cerebrospinal fluid.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 13	• I believe the project is well planned and designed to meet the objectives of the CLIN2 PA and to achieve the meaningful outcomes that will support further development of this therapeutic candidate. • Overall, the project is well designed. The applicant has significantly enhanced the manufacturing strategy and process aspect of the application. The applicant has revised the release specifications as requested. They have also removed the FISH assay assessing Chromosome 19 trisomy - eliminating this step is expected to reduce the rate manufacturing failures. • The trial is well-planned and designed vis-a-vis catheter placements, administrations, and biological monitoring. • The only major concern is the maintenance of lot-to-lot manufacturing consistency during the clinical trial. The applicant proposes up to five separate manufacturing lots to support dosing in the trial but has minimal release and in-process monitoring criteria. I

	recommend that the applicant develop a more comprehensive panel of testing criteria to enable lot-to-lot comparability throughout the trial. ● The timeline and scope of work in general appear to be appropriate and demonstrate the level of urgency that is commensurate with CIRM's mission. ● The proposal appears to be well planned and designed. ● While the applicants did not completely/satisfactorily respond to all queries, they did provide additional information.
No: 2	*none*
GWG Votes	**Is the proposal feasible?**
Yes: 15	● Preliminary human, animal and GLP data support the feasibility of this project. ● The project is feasible. The teams have considered several major risks, including the potential for manufacturing failures and clinical holds, and have designed sound contingency plans to address these potential risks. ● The Key Personnel appear to be qualified. They have demonstrated success working together on other CIRM funded proposals. ● The timeline and intended objectives are appropriately aggressive and are likely to be achieved within the proposed timeline. ● The proposal appears to be feasible. ● The groups all have experience in clinical research and it appears they would be able to accomplish the goals of the trial. ● Aggressive timeline but may be feasible based on their experience.
No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 15	● The proposal provides a clear and robust plan for outreach and study participation by underserved and disproportionately affected populations. ● The outreach efforts and planned inclusion of underserved populations for this study are also in line with the expectations of CIRM. ● The team has done a great job providing plans for outreach and engagement to enroll patients from diverse backgrounds as part of the proposed clinical trial. ● The proposed clinical sites and planned outreach efforts to underserved populations are excellent. ● Appropriate attention has been paid to serving the needs of underserved communities.
No: 0	*none*

DIVERSITY, EQUITY, AND INCLUSION IN RESEARCH

Following the panel's discussion of the application, the patient advocate and nurse 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 and nurse 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 & Nurse 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	1	● Their outreach plan will ensure the diversity so necessary in this trial.
6-8: Responsive	2	*none*
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*