June 22, 2026

California Institute for Regenerative Medicine
Application Review Subcommittee

RE: CIRM CLIN2-19526 "AAV Immuno-Gene Therapy for High-Grade Glioma"

Deer esteemed members of the CIRM ARS,

I am writing as CEO of Siren Biotechnology and PI of CLIN2-19526 to thank the GWG and CIRM for their deeply thoughtful review of our application and for recognizing the exceptional merit of SRN-101 for adults with recurrent high-grade glioma. We were grateful to see the committee recognize the urgent unmet need, the strength of the scientific rationale, our completed GMP drug product, and the feasibility of advancing this first-in-human Phase 1/2 trial.

We also took the review comments provided seriously. Since our January CLIN2 submission, we have already moved quickly to address the key concerns raised by reviewers, because that is what this program and these patients deserve.

First, reviewers noted concern that neurosurgical expertise was not sufficiently visible in the application. We agree that neurosurgical execution is central to this trial and want to clarify the structure of our team. The three site PIs are world-class clinical neuro-oncologists responsible for patient selection, trial conduct, and patient safety oversight. Neurosurgical delivery is supported separately by the experienced neurosurgical teams at each clinical site. At our lead site, UCSF, Drs. Manish Aghi and Jacob Young have already been advising us on surgical protocol development, catheter placement strategy, and intraoperative risk management, and will continue to support the trial as it moves forward.

Second, reviewers expressed concern that Siren may be too small to oversee a complex clinical program. We wish to clarify that Siren is headquartered in San Francisco with in-person laboratory and office space, and since submission we have already substantially strengthened our clinical execution team. We recently hired a Head of Regulatory, Head of Quality Assurance, Head of Pharmacovigilance, and Head of Clinical Operations. We have also initiated work with CTI, our clinical CRO, which brings a dedicated medical monitor, clinical operations team, pharmacovigilance infrastructure, data management, monitoring, regulatory documentation, and project management support. Our company is capital efficient and intentionally lean but not thin: Siren provides all the key scientific, strategic, and Sponsor oversight, while experienced clinical trial infrastructure supports execution.

Third, reviewers raised several questions about protocol clarity, including DLT management, eligibility criteria, statistical analysis, interim analysis, and trial timeline. Since submission, Siren and our clinical team have prepared a revised protocol that directly addresses these items and is being prepared for IRB submission. The revisions clarify DLT management and dose-escalation governance, eligibility across prior radiation and chemotherapy regimens, tumor type stratification, interim analysis between the Phase 1 and Phase 2 portions, statistical analysis, and enrollment contingency planning. Dr. Nicholas Butowski, Trial PI and UCSF Site PI, has submitted a separate letter of support to you addressing the clinical soundness and feasibility of the revised protocol and our program.

Fourth, reviewers noted concern that CED delivery may limit access to major academic centers. We understand the concern, but believe it should be interpreted in the context of how high-grade glioma care is delivered in practice. Patients with recurrent high-grade glioma who are candidates for first-in-human trials are already referred to hospitals with neurosurgical centers. CED is an established and increasingly standardized neurosurgical delivery method at these centers, and the single-procedure nature of SRN-

101 is meaningfully less burdensome than repeated dosing regimens. Dr. Paul Larson, Chief Medical Officer of ClearPoint Neuro and a UCSF neurosurgeon, has submitted a separate letter addressing the real-world feasibility and expanding availability of MRI-guided CED.

Finally, reviewers noted that our initial eligibility criteria limit generalizability. That is true, and it is intentional for a first-in-human intracranial gene therapy trial. Our first responsibility is to generate clean, interpretable safety and preliminary efficacy data in a well-defined patient population. As SRN-101's safety and activity profile becomes established, our goal is to rapidly broaden eligibility and expand access. That is the entire reason Siren was founded: to build an AAV gene therapy platform that is powerful enough for devastating tumors like high-grade glioma, but standardized enough to eventually reach many more patients than traditional bespoke gene therapies.

CIRM's prior TRAN1 support was transformative in helping us get SRN-101 from concept through IND clearance and GMP drug product release. This CLIN2 award is the next critical step: bringing SRN-101 to patients for the first time. We are ready to execute the trial, we have strengthened the team, and we have already addressed the issues raised during review.

Thank you for your thoughtful consideration and for CIRM's continued commitment to bold, patient-centered regenerative medicine in California.

With immense gratitude from the entire rare disease and gene therapy fields,

Nicole K. Paulk, PhD
CEO, Founder, President
Siren Biotechnology
CLIN2-19526 PI