June 12, 2026

Members of the Application Review Subcommittee
California Institute for Regenerative Medicine
601 Gateway Blvd, Suite 400
South San Francisco, CA 94080

Re: Letter of Support for PDEV-19728, "AAV Gene Therapy for Brain Metastases"

Dear Members of the Application Review Subcommittee,

I am writing with my staunch support of Siren Biotechnology's CIRM PDEV-19728 application, "AAV Gene Therapy for Brain Metastases." I serve on Siren's Scientific Advisory Board and have more than 20 years of regulatory experience in biopharmaceutical development, including senior regulatory leadership roles in gene therapy. I am writing specifically to provide regulatory perspective on one of the central concerns raised in the review: whether a tumor-agnostic basket trial strategy for SRN-101 in brain metastases is too ambitious or insufficiently grounded for this stage of development.

From a regulatory perspective, the SRN-101 tumor-agnostic strategy is not an overextension of the program; but an approach that capitalizes on the molecular mechanisms of tumors and the clinical problem it is designed to address. SRN-101 is not a systemic targeted therapy whose activity depends on a specific oncogenic driver or tumor lineage. It is a locally delivered AAV immuno-gene therapy designed to induce sustained expression of an immunomodulatory cytokine within the intracranial tumor microenvironment. The therapeutic hypothesis is therefore tied to the site of disease, route of delivery, and local biologic effect within the brain, not to a single primary tumor histology. For brain metastases, where multiple solid tumors converge on the same clinically difficult intracranial compartment, a basket strategy is scientifically and regulatorily feasible and coherent.

Regulatory agencies routinely evaluate development strategies that begin with a mechanistically justified, clinically focused population and then refine cohort structure as data emerge. A brain metastases basket trial can be designed with appropriate safeguards: histology-defined cohorts, dose-escalation controls, stopping rules, imaging-based response assessments, safety oversight, and prespecified criteria for expansion or closure of individual cohorts. It is a disciplined clinical development framework for a therapy whose mechanism is intentionally not restricted. by histology Regulators expect programs to demonstrate innovation without exceeding what is scientifically and or operationally supportable and to maintain both scientific rigor and credibility with regulators.

There is also meaningful precedent in neuro-oncology for complex, multi-arm, basket, adaptive, and platform-style clinical trial designs. GBM AGILE demonstrated that the brain cancer field can support sophisticated trial designs across multiple sites, with centralized operational coordination and adaptive decision-making. A brain metastases basket trial enrolling across primary tumor origins is not conceptually more difficult than those efforts; in some respects, it is more tractable because the investigational product, route of delivery, and treated anatomic compartment remain consistent, while individual histology cohorts can be evaluated separately.

From a regulatory perspective, Siren is also not starting from zero. FDA has already reviewed and cleared Siren's IND for SRN-101 in a closely related adult CNS oncology indication. The brain metastases program uses the exact same Drug Product (including the construct, capsid, formulation) and intracranial delivery approach, creating a meaningful regulatory foundation for safety monitoring,

delivery feasibility, product characterization, and nonclinical bridging. The proposed PDEV work is therefore not intended to establish an entirely new platform de novo; it is intended to extend an existing CNS-directed SRN-101 platform into a major unmet clinical indication using a rational and well designed and staged regulatory strategy based on clinical data.

I recognize that the reviewers identified areas where the plan should be refined, including careful definition of the initial clinical population, use of prior adult CNS oncology data, and thoughtful gating of future expansion. Those are exactly the types of issues that can be addressed through the preclinical PDEV mechanism and through continued regulatory guidance. There are not, in my opinion, reasons to conclude that the basket strategy is infeasible. On the contrary, CIRM support would allow the team to generate the specific metastasis-focused data, FDA alignment, and operational refinements needed to make the eventual IND submission in the late PDEV phase stronger, more efficient, and more clinically meaningful.

In conclusion, I believe this application is highly aligned with CIRM's mission for the development of , innovative, safe and efficacious gene therapy product... Specifically, brain metastases remain a devastating and underserved complication of cancer, and there are no approved gene therapies or locally delivered biologics of any kind designed specifically to address this intracranial disease setting. SRN-101 represents a differentiated therapeutic strategy that leverages California-based innovation in AAV gene therapy, CNS delivery, and translational oncology. It is precisely the kind of high-risk, high-impact program that can change the trajectory of a field if given the opportunity to generate decisive data. The benefits of this approach can be determined in a basket trail design.

For these reasons, I strongly support funding of PDEV-19728. The regulatory path is navigable, the tumor-agnostic strategy is scientifically justified, and the proposed PDEV work is the appropriate next step to determine whether SRN-101 can address a major unmet need for patients with brain metastases.

Sincerely,

Dr. Sharon Kaye Spratt

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