

Dear Members of the CIRM Board,

Re: Support for Application #CLIN2-20389 — Phase I Clinical Trial of a Trispecific CAR T-Cell Therapy for Multi-Antigen Targeting in CNS and B-Cell Lymphomas

I am writing in strong support of Application #CLIN2-20389, *Phase I Clinical Trial of a Trispecific CAR T-Cell Therapy for Multi-Antigen Targeting in CNS and B-Cell Lymphomas*. We serve as Program Directors of Community Care Centers of Excellence (CCCE) in the Central Valley and the Inland Empire & Desert Region (CHS CCCE and LLUH CCCE), which anticipate collaborating on this study as a point-of-care manufacturing and treatment sites.

We would like to specifically address two concerns raised during scientific review: first, the feasibility of extending point-of-care manufacturing and CAR T-cell therapy to centers outside traditional large academic cellular therapy programs; and second, the ability to establish manufacturing comparability across multiple point-of-manufacturing sites.

Point-of-care feasibility and readiness of CCCE sites

One reviewer questioned whether non-specialty centers would have sufficient resources and training to safely execute this approach and noted that substantial education and outreach might be required. Another similarly expressed concern that community centers may lack the time and resources needed to learn a decentralized manufacturing approach.

These are important considerations for broad dissemination of point-of-care CAR T-cell therapy. However, the planned collaboration with CIRM CCCEs substantially mitigates this concern because these CCCEs are not starting as inexperienced community sites. They represent deliberately developed, CIRM-supported centers with established cellular therapy, clinical research, multidisciplinary care, workforce development, and quality infrastructure. Indeed, CIRM's CCCE framework specifically calls for centers with demonstrated clinical research capability and infrastructure to conduct FDA-authorized cell and gene therapy trials while building the workforce required to expand access beyond traditional academic centers.

At CHS, for example, our cellular therapy program is already operational and has successfully delivered various commercial CAR T-cell therapies in the Central Valley. Our infrastructure includes apheresis, cellular product handling, ambulatory infusion, inpatient oncology, pharmacy, laboratory services, clinical research, patient navigation, social work, and direct access to acute hospital care. Our CAR T program was developed

through several years of multidisciplinary training, including collaboration with UCSF's cellular therapy program. We established institution-wide pathways for recognition and management of CAR T-associated complications.

Our CCCE proposal goes considerably further. Over the award period and beyond, CHS is committed to providing clinical support across the entire trial continuum, including patient identification, screening, pretreatment evaluation, therapy administration, post-treatment monitoring, and long-term follow-up.

Equally important, our CCCE has a formal partnership with the UC Davis Alpha Clinic and GMP facility specifically for workforce qualification, manufacturing technology transfer, quality management, and regulatory readiness. Personnel from CCCEs will undergo structured training in closed-system cellular manufacturing, aseptic technique, GMP documentation, quality control, and cleanroom operations, with competency assessments and protocol-specific simulations. The program also incorporates ongoing multidisciplinary education, including physician and nursing training, cellular therapy didactics, workforce-development pathways, and formal knowledge sharing with Alpha Clinics and other CCCEs.

Loma Linda's University Division of Transplant and Cellular Therapy/Hematological Malignancies is FACT accredited for adult and pediatric autologous, allogeneic, and immune effector cell therapy and already provides CAR T-cell therapy. Loma Linda University is also an active CIRM-funded CCCE specifically charged with expanding cell and gene therapy trials and developing local manufacturing capacity in the Inland Empire and Desert Region. Similarly, LLUH CCCE has an identical formal partnership with the UC Davis Alpha Clinic and GMP facility specifically for workforce qualification, manufacturing technology transfer, quality management, and regulatory readiness, personnel training as outlined before under CHS CCCE section.

Thus, the proposed decentralized model builds upon a network of selected centers that already possess substantial cellular therapy and clinical-trial capabilities and then adds structured technology transfer, competency-based training, quality oversight, and manufacturing infrastructure.

Therefore, achieving primary objective of CIRM to expand and allow access to cell and gene therapy to such underserved communities that are not located in large metropolitan areas

Manufacturing comparability across point-of-care sites

The reviewers also appropriately emphasized the importance of demonstrating comparability among drug-product lots manufactured at NIH and additional point-of-manufacturing sites, particularly if clinical data from patients treated with products manufactured at different locations are to be evaluated together.

We agree that this issue should be explicitly addressed prospectively. However, multi-site comparability is not an unanticipated problem for the CCCE manufacturing model. In fact, the CHS and LLUH CCCE manufacturing plans were deliberately designed around this requirement.

Our collaboration with the UC Davis GMP facility includes transfer of closed-system CAR T-cell manufacturing SOPs to CHS and LLUH, supervised GMP-compliant training and qualification runs, comprehensive product release testing, and joint review of manufacturing documentation specifically to develop a regulatory-grade comparability package. This is followed by formal qualification of the manufacturing environment and equipment through Installation, Operational, and Performance Qualification, with CHS and LLUH operating within a shared quality framework and centralized oversight model.

Detailed plans and collaborations with UC Davis are outlined in our CIRM funded CCCE grants for CHS and LLUH.

For CLIN2-20389, this infrastructure provides a practical framework for managing the concern raised by the reviewers. A multi-site manufacturing strategy can operate under a common master manufacturing process, harmonized SOPs and batch records, standardized raw-material and equipment specifications where applicable, common release assays and acceptance criteria, qualified operators, and unified quality-review processes. Each new point-of-manufacturing site can undergo engineering, and qualification runs before clinical production, with predefined comparability testing against the lead manufacturing site.

The scientific opportunity presented by CLIN2-20389 therefore extends beyond evaluation of an innovative multi-antigen CAR T-cell therapy. It provides an opportunity to demonstrate a scalable model in which cellular therapies can be manufactured and delivered closer to patients without compromising manufacturing rigor, patient safety, or data integrity in addition to increased affordability and cost reduction to the health care system. This objective is closely aligned with CIRM's investment in the CCCE network and its goal of expanding access to cell and gene

therapies across California. CHS and Loma Linda were both selected and funded as CCCEs to expand precisely this type of regional capability.

The reviewers have identified issues that deserve careful prospective planning, particularly around site qualification, workforce education, quality oversight, and comparability. In our view, however, these are **addressable implementation requirements rather than fundamental limitations of the proposed point-of-care strategy. The infrastructure, partnerships, and quality systems now being established through the CIRM CCCE network provide a strong mechanism for addressing them.**

We therefore strongly support Application #CLIN2-20389 and believe that collaboration with qualified CCCEs can both strengthen the proposed clinical trial and help establish an important model for safe, reproducible, and scalable decentralized CAR T-cell manufacturing and delivery.

Thank you for your consideration.

Sincerely,

Signed by:

Haifaa Abduthaq

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Signed by:

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