CLIN2 AWARDS

9/24/26

$56,247,796 GWG RECOMMENDED

$44,247,797 CIRM TEAM RECOMMENDED

$160,000,000 AMOUNT AVAILABLE

APP #	TITLE	BUDGET REQ	GWG Recmd	CIRM Recmd	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	Resub?	Previous CIRM Funding	Disease Indication
CLIN2-20316	In Utero Stem Cell Transplantation to Prevent Bone Marrow Failure and Cancer in Fanconi Anemia	$11,999,999	Y	N	90	90	2	85	92	15	0	N	Y	Fanconi anemia
CLIN2-20416	A Phase 1 study of an engineered Treg cell therapy in adults with recently diagnosed Type 1 Diabetes	$7,766,382	Y	Y	90	90	3	85	95	14	0	N	N	Type 1 diabetes
CLIN2-20392	First-in-human trial for a novel epigenetic therapy for FSHD targeting D4Z4 epigenome	$8,000,000	Y	Y	87	87	2	84	90	14	1	Y	N	Muscular dystrophy
CLIN2-20291	Phase 2 Open-Label Single-Arm Trial in Participants With Refractory Moderate-to-Severe SLE With Lupus Nephritis	$15,000,000	Y	Y	86	86	4	80	93	10	4	N	Y	Lupus nephritis
CLIN2-20409	An RNA Splicing and Base Editing Inhibitor to Target Cancer Stem Cells in Refractory Myeloid Malignancies	$5,546,253	Y	Y	85	87	2	85	92	15	0	N	Y	Blood cancers
CLIN2-20350	Optogenetic Therapy for Treatment of Stargardt Disease	$7,935,162	Y	Y	85	87	3	85	95	13	0	Y	Y	Stargardt disease
CLIN2-20389	Phase I Clinical Trial of a Trispecific CAR T-Cell Therapy for Multi-Antigen Targeting in CNS and B-Cell Lymphomas	$14,999,558	N	N	84	83	2	80	85	3	11	N	Y	Lymphoma
CLIN2-20454	An Oral Therapy to Inhibit Cancer Stem Cells	$8,418,240	N	N	80	79	4	70	85	1	14	N	Y	Colorectal cancers

Application #	CLIN2-20316
Title (as written by the applicant)	In Utero Stem Cell Transplantation to Prevent Bone Marrow Failure and Cancer in Fanconi Anemia
Therapeutic Candidate (as written by the applicant)	Maternal BM-derived CD34-selected HSPCs transplanted by in utero hematopoietic stem cell transplantation (IUHSCT) to fetus with Fanconi Anemia
Indication (as written by the applicant)	Fanconi Anemia
Unmet Medical Need (as written by the applicant)	Postnatal allo-HSCT cures FA but requires toxic conditioning, causing secondary cancers. In contrast, prenatal maternal CD34+ transplantation (IUHSCT) prevents FA hematolymphoid disease without immune ablation or genotoxic conditioning, reducing morbidity and improving life quality for patients.
Major Proposed Activities (as written by the applicant)	• Initiation of Start-up Activities • Clinical Testing: Evaluate and Treat Patient 1 at clinical site #1 • Clinical Testing: Complete and Evaluate Phase 1 at clinical site #1 • Clinical Testing: Open Phase 2 and clinical site #2 • Evaluation of Clinical and Research Objectives
Statement of Benefit to California (as written by the applicant)	This research will benefit California by establishing a curative treatment for Fanconi Anemia, significantly reducing long-term healthcare costs associated with disease management and complex transplant complications. Furthermore, the potential for a Rare Pediatric Disease Designation and a subsequent Priority Review Voucher could generate substantial non-dilutive capital, fostering economic growth and cementing the State's position as a global leader in regenerative medicine and fetal therapy.
Funds Requested	$11,999,999
GWG Recommendation	**(85-100): Exceptional merit and warrants funding, if funds are available**
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: 90

Up to 15 scientific 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.

Mean	90
Median	90
Standard Deviation	2
Highest	92
Lowest	85
Count	15
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	15
Tier 2 (1-84): Not recommended for funding	0

FINAL 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.

Key Strengths and Weaknesses

- Mechanistically elegant safety advantage by exploiting natural fetal immune tolerance, the approach avoids chemotherapy/radiation conditioning entirely — the single biggest driver of long-term toxicity in current FA treatment. This is a genuine safety differentiator.
- The only alternative therapy is bone marrow transplant, which comes with substantial co-morbidities. This therapy would impact all genotypes of the disease, offering a strong potential value proposition.
- Increase in final score attributed to clear unmet need but most specifically that this could be a potential standard of care for patients with Fanconi Anemia. By treating patients in utero, that could help alleviate challenges associated with HSCT.
- Devastating disease, needs are great. Compelling project.
- Key Strength - the proposed therapeutic approach (in utero HSCT) uses maternal BM-derived HSPCs (donor accessibility, reduced risk of rejection) and is expected to prevent the onset of progressive hematopoietic failure.
- Key Strength - no use of immune suppression or myeloablative conditioning.
- Key Strength - this treatment is not genotype dependent.
- Strong team and clinical sites, good plan for FA community outreach and collaboration, early treatment to reduce future treatments with high risk is beneficial, good regulatory and application rational for mechanism, pre-clinical and manufacturing.
- IND approval is received, with IRB submission prepared.
- Key Weakness - risk to maternal-fetal pair from performing transplant (pregnancy complications, pre-term delivery, etc.).
- The operational complexity of coordinating maternal-fetal medicine, stem cell collection, cell processing, and transplantation across a narrow gestational window is recognized and supported by experienced multidisciplinary teams. The primary operational risks remain identification and enrollment of eligible prenatal patients within the required gestational window.
- The biggest challenge that remains is identifying the potential patients within the specified treatment window that could be remedied with appropriate maternal patient material.
- The pregnant population adds some extra risk but potentially derisks the child population since the transplant is done without conditioning. Risk benefit ratio appears same and possibly better for the FA patient/child. Identifying the donor patient pair remains a project risk similar to identifying a donor for the current available transplant.
- A reviewer would like to see an Orphan Drug Designation application filed soon as it can be filed at the same time as Fast Track and IND.

Value Proposition

- This proposal has the potential to fundamentally change the treatment paradigm for FA by intervening before disease progression and eliminating many of the operational burdens associated with postnatal HSCT. If successful, the approach could simplify treatment delivery while reducing resource utilization and improving patient access.
- The Sponsor addresses a genuine, otherwise-unsolvable unmet need. The current standard of care (postnatal transplant) trades bone marrow failure for near-universal secondary cancer risk by age 30–40. Gene therapy alternatives cost $3–5M and only cover one FA subtype.
- The proposed maternal-donor in utero hematopoietic stem cell transplantation (IUHSCT) offers a potentially transformative value proposition for prenatally diagnosed Fanconi anemia by shifting treatment from reactive management of established bone marrow failure to prevention before disease onset. Current postnatal allogeneic transplantation can restore hematopoiesis but requires immunoablation and frequently genotoxic conditioning in patients who are exceptionally vulnerable to DNA damage, resulting in hospitalization, mucositis, serious infections, graft-versus-host disease, transplant-related mortality and increased long-term malignancy risk. The applicant's own improved conditioning regimen still reportedly carries 33% GvHD and approximately 8% mortality.

- Strong, extremely clear rationale and value proposition for patients with all genotypes of FA, who at present the only curative treatment is allo-HSCT, which carries significant morbidity and mortality.
- There is an unmet medical need for Fanconi Anemia treatments that prevent bone marrow failure.
- Removing the risk of post-natal bone marrow failure also eliminates the need for post-natal allo-transplant, which is burdened with concomitant expense, medical complications such as GvHD, toxicities and increased risk of malignancies such as MDS, AML and squamous cell carcinomas.
- The strong value proposition is well-substantiated by data-grounded understanding of the population disparities. This is a meaningful improvement in comparison to traditional HSCT.
- Investigators also do a good job of placing the proposed therapy in context of other innovations designed to reduce toxicity of allo-HSCT in FA and even lentiviral gene therapy (which is only at present being performed for FANCA genotype and is $3-5 million); discuss how their post-natal strategy, funded by CIRM, is still a value-add for post-natally diagnosed FA while the IUHSCT is for prenatal diagnosis.
- If successful, this approach would substantially reduce medical resource use for patients with FA (including reducing likelihood of secondary cancers), through their lifespan and has potential to become new standard of care for FA with potential to expand to other inherited bone marrow failures and potentially hemoglobinopathies.
- A single prenatal infusion of maternal CD34-selected HSPCs could potentially establish healthy hematopoiesis and maternal tolerance without conditioning, thereby reducing patient morbidity, caregiver burden, prolonged isolation and downstream healthcare costs while applying across all FA genotypes rather than only FANCA. The use of the mother as donor, an FDA-authorized protocol and a procedure analogous to established fetal transfusion support practical implementation at specialized centers.
- In addition, the feasibility and practicality of patient & healthcare provider uptake is great compared to current treatment option of HSCT as in utero is less invasive. Also potential payor cost is less than that of a traditional HSCT.
- Market analysis: they assume 30% newborn FA patients will have access to the treatment by year 5. Trials of other hematolymphoid diseases will begin in year 3 and can cover 5% of U.S. patients by year 5. The treatment can be expanded to the international market beginning in year 4. At the estimated per patient cost by the end of year 5 the combined revenue from the U.S. and the international market will reach $62 million, which can set up a stage of accelerated growth in the international market.
- Uptake of this therapy will likely be constrained by the need for timely prenatal diagnosis, maternal bone marrow harvest, specialized fetal-treatment infrastructure and the ethical and perceived procedural risks of intervening during pregnancy. Overall, the potential patient and system benefit is very high, but definitive superiority over improved postnatal transplantation will require durable multi-lineage engraftment, reduced subsequent transplantation requirements and evidence that hematologic—and ideally malignancy-related—outcomes are materially improved.
- The uptake of current FA treatments on the patients themselves is a delicate balance of risk benefit ratio. The timing and route of administration of this proposed treatment, and the procedural burden being on the "healthy" mother, is a unique solution to the risk benefit ratio related to FA patient treatment options.

Rationale

- The scientific rationale is strong and biologically coherent: the fetal immune system provides a window in which maternal cells may engraft without conventional immunosuppression, while healthy DNA-repair-competent donor HSPCs should have a progressive selective advantage over intrinsically unstable FA HSPCs. The indication is particularly well chosen because donor cells need not correct every somatic manifestation of FA to meaningfully prevent bone marrow failure, immunodeficiency and hematologic malignancy, and evidence from somatic reversion and unconditioned FANCA gene therapy supports the principle that corrected HSPCs can outcompete FA-deficient cells.
- The applicant is proposing in utero HSCT of maternal BM-derived CD34+ hematopoietic stem and progenitor cells (HSPCs) as an alternative for all FA genetic subtypes. One of the key features of this approach is that IUHSCT leverages the immunologic immaturity of the fetus and natural fetal tolerance to maternal antigens to achieve durable, multi-lineage engraftment without any toxic conditioning. They also hypothesize that the healthy maternal HSPCs will have an engraftment advantage (unlike in alpha thalassemia, FA fetuses present a highly receptive 'empty' niche. Because FA is characterized by progressive BM hypocellularity, healthy donor HSPCs do not have to compete with a crowded endogenous population) and prevent hematolymphoid disease in FA settings without immune ablation and DNA-damaging conditioning, thereby reducing transplant-related morbidity and mortality and improving QOL.
- Infusing CD34+-enriched stem cells from the mother's own bone marrow directly into the fetus, in fetuses prenatally diagnosed with Fanconi Anemia (FA). This exploits the fetus's natural immune tolerance, entirely avoiding the toxic chemotherapy/radiation conditioning required by postnatal transplants.

- Post-natal allogeneic transplantation is standard of care for symptomatic patients; IUHSCT is a pre-natal intervention on asymptomatic fetus - effectively the same procedure, but with benefits such as donor accessibility, no use of immunosuppression or ablation, low to no risk of GvHD.
- There is a "window of fetal ontogeny" during gestation when gestational trafficking of cells results in bidirectional micro-chimerism, which is fundamental to establishing maternal-fetal tolerance. Use of maternal bone marrow for transplant takes advantage of this in utero biology to permit engraftment of allogeneic maternal cells without conditioning or immunosuppression.
- Failing FA cells are out-competed by healthy HSPCs, allowing the fetus to establish a functional, DNA-repair-competent hematopoietic system.
- If sufficient levels of chimerism are not achieved to establish a functional hematopoietic system, low levels of donor hematopoietic chimerism can induce donor-specific tolerance, which would permit post-natal dosing of HSPC from the same donor with minimal conditioning.
- Clinical rationale is supported by preclinical data in multiple FA mouse models (high engraftment and disease mitigation) and supported by known complications of current allo-HSCT approaches and even approaches to reduce toxicity of conditioning; also supported by clinical experience of with IUHSCT for alpha thalassemia showing safety and feasibility in a CIRM-funded Phase 1 trial.
- The approach is supported by clinical experience with X-SCID and other diseases that rely on curative engraftment, current practice of in utero transfusions, an alpha-thalassemia clinical study, mouse studies and large animal studies.
- The application is supported by directly relevant, same-team, same-graft-characteristics prior human data: the alpha-thalassemia IUHSCT trial reported no fetal adverse events, no GvHD, and no maternal sensitization in 6/6 treated fetuses - meaningfully de-risking the safety profile of the FA proposal even though durable engraftment was not achieved in that earlier trial.
- The strategy builds upon an FDA-approved Phase 1/2 protocol and prior clinical experience with a similar IUHSCT platform.
- Rationale for mechanism is clear, preclinical studies are supportive, and the reviewer's concerns for maternal/fetal safety risk are lessened with the reference to the alpha-thalassemia trial. Having this experience, both institutionally and key personnel will be critical to the success of this trial.
- Within the context of IUHSCT, every fetus is either naturally tolerant to its mother or can be rendered so through in utero transplantation (strong rationale for using mother); also based on preclinical animal and clinical experience with IUHSCT, there is a very low clinical suspicion that GvHD would develop in fetuses, thus, the team does not plan to use T cell-depleted grafts (also aligned cell doses to reduce risk of).
- Strengths and weaknesses are well-described. They acknowledge that this strategy will only be available for FA with prenatal diagnosis but also that strategy could encourage development of maternal blood tests for FA; the strategy may not eliminate all risks of FA (doesn’t eliminate all FA hematopoietic cells; it doesn’t correct systemic FA potential for maternal sensitization; that said, one could use alternative donors if future HSCT is needed).

Project Plan and Design

- The project plan is generally appropriate for an early Phase 1/2 trial and includes the major activities needed to treat and follow about a dozen maternal–fetal pairs, including prenatal screening, maternal marrow procurement, GMP CD34 selection, fetal infusion, serial safety and chimerism monitoring, immune-tolerance studies and two-year hematologic evaluation.
- The investigators have translated prior fetal therapy experience into a realistic clinical execution plan rather than developing an entirely novel operational model.
- Leveraging an already-approved IND and an experienced regulatory manufacturing lab infrastructure substantially de-risks the startup timeline relative to a first-in-kind program.
- Directly relevant safety precedent - the same product, procedure, and manufacturing pipeline were already used in a related CIRM-funded alpha-thalassemia trial, which showed no safety concerns or GvHD — a meaningfully de-risked starting point versus a true first-in-human procedure.
- The efficacy bar may be too low to prove real clinical benefit. The endpoint was negotiated down from FDA's initial ask of ≥10% chimerism to ≥1% — meeting that bar does not necessarily mean the therapy will actually prevent bone marrow failure or cancer; the real long-term outcomes that matter will not be measurable within the trial's timeframe.
- The IND is cleared which reduces regulatory risk; Fast Track designation has been granted in recognition of rare disease / unmet medical need; future plans to seek Orphan Designation and RMAT are appropriate.
- The use of maternal donor BM levels the playing field of race and ethnicity – non-caucasian patients will not experience the greater probability of not finding an HLA matched donor.

- Utilizing two centers to complete treatment of over ten maternal-fetal pairs makes sense; starting with one based on their prior institutional experience with the procedure and adding a second, both sites leveraging manufacturing expertise from the first institution is appropriate.
- Reasonable participant numbers. Plus, the team are experienced with this community.
- Requesting CIRM funding to initiate study and complete the treatment of over ten maternal-fetal pairs; clear milestones and feasible timeline.
- The timeline seems reasonable with over a half dozen patients identified over the past ~year that would potentially qualify for treatment.
- No concerns about manufacturing. Both sites/manufacturing facilities have experience in this type of manufacturing. Concern for reagents is valid and they appear to have secured what is needed for the clinical trial.
- Clinical GMP manufacturing has been derisked by having produced products for alpha-thalassemia, engineering runs and use of industry-vetted technology for cell enrichment and selection is appropriate.
- Manufacturing risk is moderated by prior use of the same general product and process in the alpha-thalassemia trial, an established cellular-therapy facility, defined release testing and reported product stability for up to 72 hours at 4°C.
- Clinical Endpoints are well-defined and even the base case endpoint (is >1% total donor chimerism in the UCB obtained at birth in >50% of transplanted patients), which is supported by their preclinical studies, would represent an improvement over current, given it should confer tolerance to maternal cells so that a postnatal “booster” allo-HSCT from the same maternal donor could be performed using minimal conditioning, if required. Optimal endpoint is engraftment after IUHSCT leads to >20% donor chimerism at 2yo in 100% of transplanted patients. This level would be expected to prevent BMF, immune deficiencies, and dysplasia.
- Feasible base and optimal CD34+ stem cell doses, based on both pre-clinical mouse studies and clinical alpha-thalassemia trial.
- The safety base-case and optimal-case endpoints are based on the prior IUHSCT for alpha-thalassemia trial using maternal-derived CD34-selected HSPCs, and reasonably defined, including fetal survival, GVHD and immune response-clearly defined and agreed upon safety stopping rules and discussion with FDA; clearly defined alternatives to UCV administration; well-defined risk mitigation strategies.
- Well thought out enrollment strategy, evidence-based accrual predictions, have validated manufacture and clear plan for SOPs, clear contingency plans and mitigation strategy for low enrollment-discuss having had over a half dozen patients with a prenatal FA diagnosis referred to center over the last several years (feasibility of achieving the enrollment target).
- The largest weakness is enrollment feasibility: FA is rare, prenatal diagnosis is uncommon, eligibility is restricted to a relatively narrow gestational window, participation requires both fetal eligibility and a medically suitable maternal donor, and only two highly specialized California sites are planned.
- Patient recruitment and outreach plans are initiated and educational materials will be multi-lingual; recruitment delays are a risk.
- The plan would be strengthened by more explicit enrollment triggers, quantified referral funnels, predefined activation of additional fetal-treatment sites, clearer budget contingency for prolonged enrollment and more detailed decision criteria distinguishing an inadequate platform from an inadequate dose or administration strategy.
- This reviewer is curious why Orphan Designation was not requested at the time of IND since FastTrack and Orphan can be submitted at this time and they were successful in getting Fast Track.

Project Team and Resources

- The team is an important strength and appears unusually well-matched to the complexity of this project. The PI provides sponsor-investigator leadership and expertise in FA, hematopoietic transplantation and clinical translation; additional key personnel lead fetal and maternal clinical operations at the proposed clinical sites; a named person oversees manufacturing; and dedicated personnel are assigned to project management, regulatory execution, data management, immune monitoring and clinical follow-up. The collaboration brings together two institutions with established fetal-treatment programs, pediatric transplantation expertise, cell-processing facilities and prior experience conducting the CIRM-supported alpha-thalassemia IUHSCT trial, thereby reducing both procedural and regulatory learning curves.
- Team has appropriate technical expertise for this project - manufacturing, clinical, regulatory, project management.
- Outstanding, well-positioned multi-institutional team; The co-PI and the collaborating team provide the expertise to expand this technology to fetuses with FA.
- Experienced project teams and manufacturing facilities. No concerns. This application appears to have strong collaboration support from experienced CA research institutions and nonprofit organizations.

- Reuse of the prior alpha-thalassemia IUHSCT trial's regulatory relationships and consent infrastructure is a credible, low-risk path to timely IRB and FDA engagement.
- The study benefits from prior CIRM-funded fetal therapy experience, FDA IND approval, centralized safety oversight with a DSMB, and collaboration among institutions with demonstrated expertise in fetal interventions, substantially reducing operational execution risk.
- They have an experienced clinical and manufacturing team, with prior experience in similar clinical trials for alpha-thalassemia.
- Product manufacturing will occur at a university GMP facility with support of several collaborating centers, core facilities, and the laboratory of the PI.
- No concerns regarding ability to start-up, manufacture, execute, expand to other sites.
- Strong clinical sites.
- Dedicated, non-overlapping operational roles are named beyond the scientific leads: two site project managers, a regulatory specialist, a genetic counselor, a lead scientist, a data project manager, and a budget/compliance manager, which suggests the coordination burden of a two-institution trial has been consciously staffed.
- Project activities will be coordinated through several named centers affiliated with the proposed clinical sites.
- The team and resources appear adequate for the successful completion of the proposal.

Population Impact

- The operational strategy directly addresses barriers to access by utilizing maternal donors, eliminating donor registry dependence, reducing treatment complexity, and potentially enabling earlier intervention through prenatal diagnosis.
- Using the mother as a universal donor sidesteps the well-documented racial disparity in finding HLA-matched donors (79% match rate for white patients vs. 29% for Black patients).
- At present, postnatal allo-HSCT is currently only performed once severe hematologic disease develops, which often occurs in late childhood or early teenage years; this proposal could reduce the prevent the transfusion-dependence and significant medical resource use/effects on QOL if performed intrauterine. Equity: disease occurs across all races and ethnicities and there are more than 23 genetic subtypes with diverse mutations, complicating universal treatment.
- The proposal demonstrates a thoughtful understanding of how FA diagnosis, access to specialty care and outcomes vary across affected populations. It identifies delayed diagnosis among patients without obvious congenital abnormalities, geographic and financial barriers to frequent marrow and cancer surveillance, poorer transplant outcomes in adolescents and adults, and the particular relevance of Hispanic/Latino families in California, who constitute approximately 41% of the applicant institution's FA cohort and may face higher rates of underinsurance, poverty and language-related barriers.
- Discuss how FA outcomes are affected by access barriers (under uninsured, financial, geographic, language, etc.) and relevance to California population; discuss how proposal standardizes early diagnosis, standardizes and simplifies the care and reduces long-term care needs.
- As the field progresses treatment options for orphan indications, it is a natural progression to begin looking at the potential for elimination of the disease or significant disease burden as soon as possible. If an option is available to treat the condition before the FA patient progresses to BMF or other malignancies, it would greatly improve the lives, cost, and healthcare system of FA patients.
- The Sponsor understands the trial population well - they understand the patient diversity, challenges of recruitment, expertise required for treatment to be successful, challenges of participation (and therefore provide logistical, financial support).
- The applicant grounds their understanding of population attitudes in original data - a peer-reviewed community survey (Lum et al., Prenatal Diagnosis, 2026) indicating the FA community is generally supportive of prenatal intervention - which directly addresses the criterion's call to evaluate the applicant's understanding of the affected population.
- As they are studying diverse populations, multilingual access is concretely underway (English and Spanish flyers already produced; additional languages available on request via the applicant institution's translation services) and bilingual research coordinators are planned for consent and enrollment support.
- Diverse patient enrollment table reflective of FA population by race/ethnicity/sex/age.
- Engagement with community and advocates as part of the design and implementation of the trial is important and could be what helps reach target enrollment.
- Good support of patients in delicate pregnancy state and incorporates lots of support orgs into the design of the project.
- Discuss financial support, patient navigation, virtual screening and telehealth.

Application #	CLIN2-20416
Title (as written by the applicant)	A Phase 1 study of an engineered Treg cell therapy in adults with recently diagnosed Type 1 Diabetes
Therapeutic Candidate (as written by the applicant)	A patient-derived engineered Treg cell therapy designed to stop the immune attack that damages insulin-producing cells in type 1 diabetes
Indication (as written by the applicant)	Type 1 diabetes approximately 6 months from diagnosis, when immune damage to insulin-producing cells is still ongoing
Unmet Medical Need (as written by the applicant)	Even with modern insulin delivery and glucose monitoring, long-term blood sugar control remains difficult for people with type 1 diabetes. Poor control can lead to serious, irreversible organ damage, reduced quality of life, and life-threatening low-blood-sugar events caused by insulin treatment.
Major Proposed Activities (as written by the applicant)	• Manage clinical sites and trial execution, including oversight, safety monitoring, and visits • Oversee CRO clinical operations, monitoring, data capture, and regulatory-compliant trial conduct • Manufacture patient-specific drug product from leukapheresis through final formulation • Perform GMP quality control, release testing, and chain-of-identity logistics for drug product • Conduct protocol-specified clinical, biomarker, and immunologic assessments • Analyze clinical and biomarker data to support safety evaluation, regulatory meetings, and decisions
Statement of Benefit to California (as written by the applicant)	This project directly benefits California by enrolling patients at 3 leading California trial sites, with up to 9 California residents expected to participate. The study strengthens California's leadership in advanced cell therapy research, expands equitable access through CIRM Alpha Clinic community outreach, supports clinical workforce expertise and trial infrastructure, and lays the groundwork for future pediatric trials in California if early results support potential direct benefit.
Funds Requested	$7,766,382
GWG Recommendation	**(85-100): Exceptional merit and warrants funding, if funds are available**
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

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FINAL COMMENTS

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Key Strengths and Weaknesses

- The therapeutic candidate cells' triple genetic modification is a scientifically coherent response to specific failure modes of stability and reliance on exogenous IL-2 (with its own safety concerns) noted with previous cell therapies targeting T1D.
- Strengths: Excellent underlying scientific rationale with extensive preclinical studies; very strong value proposition in reducing the medical and financial burden of type 1 diabetes; excellent project plan with strong recruitment sites. Support by Breakthrough T1D and by Helmsley Trust is also impressive.
- Weaknesses: The autologous cell therapy means that each batch of cells must be engineered, thus there is "no economy of scale"; also, the MHC target limits the eligible patient population and precludes inclusion of certain segments of the California population.
- Strengths: Value Proposition and Rationale: The proposal addresses a significant unmet need in recently diagnosed Type 1 Diabetes with a differentiated, disease-modifying regulatory T-cell approach supported by compelling preclinical data and encouraging early clinical experience. The proposed therapy has the potential to preserve endogenous β-cell function and meaningfully improve long-term patient outcomes. Project Plan and Team: The clinical development plan is well structured with appropriate milestones, manufacturing readiness, and an experienced multidisciplinary team with demonstrated expertise in cell therapy development, regulatory strategy, and clinical execution, supporting the feasibility of the proposed Phase 1 study. Population Impact and Patient Access: The application demonstrates thoughtful consideration of future patient access, reimbursement, and affordability, with a stage-appropriate strategy that integrates patient engagement, evidence generation, and health economic planning early in development.
- Weaknesses: Project Plan and Risks: As a first-in-human Phase 1 study, clinical efficacy, long-term durability, and scalability of the therapeutic effect remain to be established. The commercial value proposition will depend on demonstrating sustained clinical benefit beyond early proof-of-concept. Population Impact and Patient Access: While the access strategy is well conceived, several reimbursement and market access assumptions will require validation through future real-world evidence, payer engagement, and longer-term clinical outcomes as the program matures.
- This approach could offer a tremendous value proposition in an indication that would impact many patients.
- Additional details provided by a disease area expert panelist were very helpful regarding the ability to meet milestones with the plans as laid out. Additional details and assurance of CRO oversight are critical to ensure timelines are met, risk mitigation is in place and planned governance to address any delays or contingencies is in place.
- The key strength from a regulatory perspective is that plans for FDA engagement and the prior FDA interactions are all reasonable and sound. The plans for FDA discussions of future trials with earlier intervention in adults and pediatrics are sound and advisable.
- The program is clinically and operationally advanced, with an FDA-cleared IND, Fast Track and Orphan Drug designations, an ongoing trial with participants already treated, activated California sites, and an established autologous manufacturing process.

Value Proposition

- Current T1D standard of care (insulin, glucose monitoring) manages symptoms but does nothing to halt the underlying autoimmune destruction of beta cells. This T cell therapeutic approach targets the root cause rather than just glycemic control.
- Because of the HLA restriction, only about 29–45% of T1D patients (depending on ancestry) are eligible.
- Type 1 diabetes (T1D) is a devastating disease requiring lifelong glucose monitoring and insulin treatment with danger of both under-treatment leading to vascular complications and over-treatment leading to life-threatening hypoglycemia. There is currently no cure for T1D, although trials are underway to develop insulin-secreting cells derived from hESC's for transplant and potential cure.

- Immunomodulatory approaches are also under development, and one such therapy, teplizumab, a monoclonal Ab (Mab) that targets the T cell CD3 antigen has been FDA approved to slow onset of T1D in subjects with stage 2 T1D, i.e. islet Ab positive but not yet requiring insulin. Other immunomodulatory approaches involve methods to increase T regulatory cells (Tregs) which could reverse the autoimmune response in T1D. Infusion of polyclonal Tregs is one such approach but has limited efficacy. Thus there is a major unmet need for effective immunomodulatory strategies for T1D.
- This proposal outlines efforts to test in a Phase 1 clinical trial a unique, engineered autologous antigen specific Treg which contains an islet-specific T cell receptor targeting a T1D autoantigen on the HLA DRB1 major histocompatibility complex (MHC). The candidate also contains a regulatory element providing inducible signaling for IL-2 secretion that favors survival of the Treg cells.
- The Phase 1 trial would enroll subjects with the HLA DRBI MHC who are in stage 3 T1D (require insulin treatment for glucose control but have some remaining islet beta cell function) and test the ability of the applicant's approach to preserve and even restore beta cell function. If successful, this would represent a major step forward in the treatment of T1D with the potential to reduce the need for insulin injections and to lead to fewer short and long term complications in subjects with T1D. This would mean a major improvement in quality of life for patients, a major reduction in burden for caregivers such as parents of children with T1D (although children would not be enrolled in the initial Phase 1 trial) and reduce the burden and expense of T1D for the health care system.
- Because the therapy is simple to administer and the side effect profile is relatively benign, the proposed approach should be quite accessible and readily taken up by patients, health care providers and the health system.
- Strengths:
    - Addresses an important unmet need by intervening early in disease progression rather than treating established insulin deficiency.
    - Potential for durable preservation of endogenous insulin production could substantially reduce lifelong clinical, caregiver and healthcare burden.
    - Access strategy appropriately recognizes payer evidence requirements, health economics and outcomes research (HEOR), real world data generation and value-based reimbursement planning from an early stage.
    - Single administration may reduce long-term treatment burden compared with lifelong insulin therapy if efficacy is durable.
- Considerations:
    - Long-term durability remains unproven and will ultimately determine payer willingness to reimburse at anticipated premium pricing.
    - Autologous manufacturing introduces complexity, scalability and cost challenges that may limit broad adoption.
    - Demonstrating meaningful differentiation versus Teplizumab and future disease-modifying competitors will be critical.
    - The relatively narrow HLA-defined eligible population may improve affordability but also introduces implementation complexity.
- The value proposition is very high. T1D affects an estimated 2 million people in the United States, with approximately 64,000 new diagnoses each year with no approved cures and only one disease modifying therapy to date.
- The therapy has achieved significant regulatory milestones, having received clearance of its Investigational New Drug (IND) application from the FDA. In addition, the program had been granted both Fast Track and Orphan Drug designations, which are expected to further accelerate its clinical development and facilitate regulatory interactions.
- Very importantly, this program is being supported by Breakthrough T1D (formerly JDRF and the world's largest global funder of diabetes research) and the Helmsley Charitable Trust which has devoted a tremendous amount of capital to type one diabetes.
- The work will support studies of the candidate T cell therapy in a pediatric population and could ultimately deliver a transformative, disease-modifying therapy for T1D, halting the autoimmune attack and preserving patients' own ability to produce insulin from residual beta cells.
- While the current specific target are patients in Stage 3 of T1D, it is expected that this treatment approach would work on Stage 1 and Stage 2 patients as well.
- It seems there may be limitations on eligible patients compared with more broadly applicable therapies. The candidate addresses a significant unmet need in T1D and could reduce long term diabetic complications, improve QOL and reduce caregiver burden. Value is compelling, but until demonstration of durable preservation of β-cell function is established, it is unknown.

- The proposed therapy has great potential to provide substantial and sustained improvement of patients with type 1 diabetes. The prospect of halting the autoimmune destruction of islet cells in early and even pre-symptomatic patient populations poses the potential of great improvement by preserving islet function, halting progression towards insulin dependence, and avoiding other sequalae of progressing diabetes.
- The therapeutic candidate addresses the underlying autoimmune process in recently diagnosed T1D rather than only replacing insulin. It has the potential to preserve endogenous beta-cell function, reduce insulin requirements, improve glycemic control, and decrease long-term complications and disease-management burden.

Rationale

- The scientific rationale is unusually coherent. Genetic modifications are intended to stabilize Treg identity, direct activity to pancreatic islets and draining lymph nodes, and provide selective IL-2-like support in the IL-2-deficient autoimmune environment.
- This is an autologous CD4+ T cell therapy, engineered with three modifications: one to lock in a stable Treg identity (natural Tregs can lose their suppressive phenotype under inflammation), an islet-antigen-specific homing specifically to the pancreas rather than acting as a blunt immunosuppressant, and a signaling switch that substitutes for IL-2 survival signals, since the inflamed T1D pancreatic environment is IL-2-deprived.
- The proposal is supported by a strong scientific rationale. Immunomodulation of T1D has already been shown to delay onset of T1D using anti-CD3 mAb in subjects with stage 2 T1D. This approach with Treg cells offers the prospect of more effective immunomodulation, including in subjects with stage 3 T1D, and thereby reducing or even eliminating their need for insulin injections to control blood glucose. Substantial evidence supports the use of Treg cells to treat T1D, but a major limitation has been the lack of availability of a durable form of Treg therapy that maintains Treg function long enough to favorably impact the autoimmune T1D process.
- The applicants' preliminary studies support their approach, regimen and route of administration, including the benefit of the inducible IL-2 secretion to preserve Treg function. The use of autologous cells to engineer the therapy is an important benefit in increasing its adoption. The therapeutic candidate is shown to increase a master regulator of Treg function.
- The application provides compelling evidence of disease modifying activity, first in a relevant mouse model. But here it must be noted that the field is replete with examples of T1D therapies that have been proven effective in mouse models, yet this effectiveness failed to translate when tested in humans.
- The extensive preclinical studies conducted on pharmacology, pharmacokinetics and toxicology are an important strength of the proposal, and set the stage for the proposed Phase 1 trial. FDA granting of "fast track" status and "orphan drug" status are favorable indicators that regulatory requirements for the trial have been met successfully.
- The biological rationale for restoring immune tolerance through engineered antigen-specific regulatory T cells is scientifically compelling and supported by preclinical evidence together with encouraging early clinical experience using polyclonal Tregs.
- The proposed engineering strategy directly addresses recognized limitations of native Treg biology, although clinical durability and reproducibility remain to be demonstrated.
- Strengths:
    - Strong mechanistic rationale targeting the underlying autoimmune pathophysiology rather than symptomatic glucose management.
    - Engineering strategy addresses known limitations of native Treg stability, specificity and persistence.
    - Prior clinical experience with polyclonal Tregs provides supportive translational evidence.
    - Early intervention is biologically well justified given preservation of residual β-cell mass.
- Considerations:
    - Clinical evidence remains early, and durability beyond initial follow-up remains uncertain.
    - Translation from engineered Tregs to reproducible clinical benefit remains an important development risk.
    - Long-term immune effects and cell persistence require continued evaluation.
    - Comparative evidence versus existing disease-modifying approaches is currently limited.
- Preclinical studies have demonstrated that the therapeutic cells are stable regulatory cells, have an immunomodulatory cytokine expression profile, and can suppress pathogenic islet antigen-specific T effector cells isolated from patients with T1D. Efficacy studies in mouse models of T1D suggest curative potential, with durable immune tolerance and preservation of insulin-producing cells.

- The goal with this approach in T1D would be to ameliorate the patient's ongoing autoimmune attack, allowing preservation of islet cell function resulting in decreased effort to control glucose, along with long-term improvement in the critical level of glycemic control.
- Early experience from the first-in-human study indicates excellent tolerability. Nonclinical pharmacology and safety data on the applicant's modified Treg approach and favorable clinical safety findings from natural sorted Treg administration to humans to date support the clinical evaluation of this candidate therapy.
- Modification and maintenance of Tregs has been a learning experience. An efficacious Treg therapy needs mechanisms ensuring Treg stability, appropriate targeting and importantly adequate IL-2 signaling support for persistence in vivo; the applicant has incorporated these learnings into their T reg product candidate.
- The candidate is designed to halt autoimmune-mediated beta-cell destruction, preserve residual insulin secretion, and reduce exogenous insulin requirements with a single administration.
- There is good overall preclinical data, including in vivo data.
- Multiple aspects require clinical confirmation; however, appropriate surrogate animal studies have been done and are supportive. The trial builds on prior clinical experience demonstrating safety and rationale for potential improved efficacy.
- The rationale is well founded in current understanding of Treg biology and employs cell and organ-type specificity as well as the potential for localized bystander effects on destructive T cells with other antigen specificities.
- Preclinical studies are supportive of both the safety and effectiveness of use of the product candidate. This is bolstered by experience with polyclonal Treg cell therapies in T1D.

Project Plan and Design

- The applicants' project plan and design are carefully described and deemed excellent. The Phase 1b protocol is already underway with subjects in cohort 1 recruited and dosed. Three California sites have been activated to participate. The plan is to carefully stage recruitment, monitoring patients' outcomes will inform entry into subsequent cohorts of patients with a goal of eventually moving from adults to children with T1D.
- The applicant did not conduct the usual range of nonclincial studies to support the first-in-human trial. The FDA reportedly endorsed a risk-based, non-animal testing strategy instead.
- Because of the structure of the engineered Tregs, the approach is limited to subjects with the MHC engineered into the the administered cells. This limits the patient population eligible for enrollment. Eligibility is also limited to subjects with stage 3 T1D of recent onset, but the applicants show evidence that this represents ~30% of recently diagnosed T1D patients. Thus, the likelihood of achieving timely full enrollment is increased, especially with the inclusion of sites outside of California with additional support from the "Breakthrough T1D" Foundation (formerly JDRF).
- The manufacturing process and analytical development are well described in the application. Budget and timeline are carefully outlined and support the likelihood of timely achieving project objectives. A number of contingencies have been anticipated, and contingency plans outlined appropriately.
- The Phase 1 study appears appropriately designed to establish safety while generating clinically meaningful signals that could support subsequent development decisions. The proposed milestones are logical, although successful execution will depend upon efficient manufacturing, enrollment and demonstration of clinically relevant durability.
- Strengths:
    - Study objectives appropriately align with Phase 1 safety and proof-of-mechanism goals.
    - Clinical endpoints evaluating insulin independence, C-peptide preservation and insulin utilization are clinically meaningful.
    - Manufacturing strategy appears integrated into the development plan.
    - Access planning appropriately evolves alongside clinical development.
- Considerations:
    - Enrollment into a narrowly defined early-stage patient population may require efficient referral pathways.
    - Manufacturing turnaround and scalability remain important operational risks.
    - Longer follow-up will likely be required to fully establish durability.
    - Clearer go/no-go criteria for later-stage development should continue to evolve as additional clinical data emerge.

- The project plans are compelling. Clearly, there has been substantial work undertaken to date for a complex task and most importantly designing ways to obviate what has caused a failure in Treg therapy approaches previously.
- The study is appropriately designed to evaluate safety, tolerability, PK, and biological activity before advancing to efficacy studies. Sequential cohort escalation introducing rapamycin only after establishing the safety of the cells alone represents a thoughtful, risk-mitigating clinical design. Biomarker development is comprehensive and should provide important translational data supporting future go/no-go decisions.
- The proposal provides relatively limited detail regarding patient recruitment strategies, screening for HLA eligibility, and contingency plans for enrollment delays. Given the narrow eligible population, these operational considerations represent important execution risks that could affect study timelines and should have mitigation plans.
- In addition to their Fast Track and Orphan Drug approvals, the applicant intends to apply for an RMAT and also intends to propose Accelerated Approval for their gene modified Tregs based on C-peptide as a surrogate endpoint predictive of long-term clinical benefit. These all demonstrate the strength of the proposal.
- The manufacturing process, the in-process and lot release criteria, stability program, and QC plans are all appropriate for early phase trials and the applicant understands the basics for BLA application.
- Manufacturing is technically complex, involving autologous starting material, multiple edits, cGMP components, selective enrichment, cryopreservation, and extensive release testing. This creates meaningful risks of manufacturing failure, long turnaround time, cost, and eventual commercial scalability.
- Execution risk is reduced because the IND is active, three California sites have been activated, initial participants have been screened and treated, and early experience supports operational feasibility.

Project Team and Resources

- The applicant team and its CRO partner are very experienced with established track records in the relevant clinical trial issues. Oversight and communication plans are well outlined. Resources are appropriate to the goals stated.
- The multidisciplinary team appears well positioned to execute an early clinical development program spanning immunology, cell therapy manufacturing and clinical investigation.
- The inclusion of early commercial and access planning strengthens translational readiness beyond many Phase 1 programs.
- Strong scientific and clinical expertise in Treg biology and autoimmune disease.
- Appropriate integration of manufacturing capabilities with clinical development.
- Commercial planning demonstrates early consideration of reimbursement and patient access.
- Development strategy reflects understanding of regulatory and payer evidence requirements.
- Commercial success will ultimately require further investment in manufacturing scale-up.
- Future evidence generation should continue incorporating payer-relevant outcomes.
- Broader implementation planning across community endocrinology settings will become increasingly important during later-stage development.
- Long-term manufacturing capacity and cost reduction strategies will remain important to maximize patient access.
- The team is very strong and more than capable to execute the project plan.
- Operational experience in multi center trials is less comprehensive than the scientific expertise. However, the investigators demonstrate substantial experience in some areas. Details for CRO oversight, vendor management, site management and governance is limited, and would need to have additional details with contingencies, risk mitigation and timelines with dependencies built in.
- The regulatory plan encompasses the manufacturing and characterization plans for early phase trials, and demonstrates awareness and preparedness for Phase 3 trials, BLA application, and commercialization.
- The team has demonstrated leadership, expertise, and staffing to complete all tasks, including former CMO experience and engagement with an experienced CMO for product manufacturing.
- Several team members have direct experience supporting licensed cellular therapies, including manufacturing stewardship and biomarker development for products such as Breyanzi, Kymriah, and Carvykti, increasing confidence in stage-appropriate execution.

Population Impact

- The proposed population will be those with a specific HLA-DR allele, a major histocompatibility complex associated with Type 1 diabetes. The incidence of this complex is mainly associated with white

individuals, mainly of northern European descent. The improvement in understanding genetic components of chronic diseases allows for potential therapies that will impact care for that specific population. The FDA has granted Orphan Drug status for the proposed indication.

- The application clearly details the proposed trial enrollment and makes clear that the nature of the Treg candidate therapy will exclude certain segments of the California patient population such as most Asians, and a substantial proportion of Blacks and Hispanics because of its limitation to subjects with a specific HLA DR allele. The presumed target population will be 85% White. This is an unavoidable consequence of the structure of the genetically modified Tregs and is well justified for a number of scientific reasons. Furthermore, if the trial is eventually deemed successful, it should pave the way for additional forms of this modified Treg approach that would be more widely applicable to additional relevant populations with T1D.
- Overall, the inclusion of over five additional U.S. sites beyond California, importantly, the majority of which, are members of the NIH-supported TrialNet for clinical studies in T1D, enhances achievement of enrollment goals. The 3 CA sites and additional U.S. sites listed above are experienced in recruiting subjects for T1D clinical trials.
- The application appropriately considers patient access and affordability; however, future implementation will require attention to equitable diagnosis, referral and reimbursement beyond specialized centers.
- Strengths:
    - Significant potential to improve long-term outcomes through early disease modification.
    - Focus on preserving endogenous insulin production aligns with meaningful patient-centered outcomes.
    - Early recognition of affordability, payer engagement and patient support strategies strengthens translational potential.
    - Potential long-term reduction in diabetes complications could generate substantial societal benefit.
- Considerations:
    - Earlier diagnosis remains a prerequisite for identifying eligible patients.
    - Specialized manufacturing and treatment infrastructure may initially limit geographic access.
    - Broad adoption will depend upon demonstrating value across diverse payer populations.
    - Continued focus on equitable identification and referral of eligible patients will be important as development progresses.
- While the first efforts here are confined to a particular allele, it is present in 29%-45% of the T1D population. As a result, there is a chance to address a significant portion of newly-diagnosed or newly-screened patients. At the same time, the findings here offer the potential to further expand the target population.
- There is limited information in the application regarding plans for participant outreach.
- The applicant demonstrates exceptional understanding of clinical burden and importance of early intervention. If successful, they would have potential to broaden applicability.
- Enrollment targets ensuring demographic diversity are not well developed or provided. There is limited operational detail about participant outreach, retention, and contingency planning if recruitment is harder than expected due to very restricted eligibility criteria.
- The applicant's strategy to apply for a variety of FDA accelerated path opportunities (RMAT, Fast Track, Orphan Drug, Accelerated Approval) demonstrates a good grasp of the T1D population, the medical challenges with advanced T1D, and the progression and symptomology of different disease stages. The applicant uses this understanding to clearly address how the product and its potential effect could reduce disease burden and improve health outcomes while reducing lifetime costs associated with T1D.
- The proposal would be strengthened by more concrete outreach and retention plans addressing travel, leukapheresis burden, time away from work or school, caregiver needs, language access, and participation costs for underrepresented communities.

Application #	CLIN2-20392
Title (as written by the applicant)	First-in-human trial for a novel epigenetic therapy for FSHD targeting D4Z4 epigenome
Therapeutic Candidate (as written by the applicant)	The therapeutic candidate is a gene therapy designed to modulate the expression of the DUX4 gene, a gene involved in the development of FSHD
Indication (as written by the applicant)	Facioscapulohumeral Muscular Dystrophy (FSHD)
Unmet Medical Need (as written by the applicant)	FSHD is a rare, complex, and disabling neuromuscular disorder characterized by progressive skeletal muscle degeneration and weakness, significantly impairing the patient's quality of life. Currently there is no cure for FSHD and only palliative care is available
Major Proposed Activities (as written by the applicant)	• Manufacture a cGMP batch of product candidate and complete Chemistry, Manufacturing, and Controls activities • Develop and validate a potency assay and biomarker assays to support clinical development • Complete a Phase 1/2 study of the candidate in FSHD Patients
Statement of Benefit to California (as written by the applicant)	Developing this gene therapy candidate will strengthen California's leadership in gene-therapy innovation, create high-skill biotech jobs, and attract new investment to state labs and manufacturing sites. Success will give Californians affected by FSHD a first disease-modifying treatment, reduce lifelong healthcare costs, and expand the state's tax base through commercialization revenues
Funds Requested	$8,000,000
GWG Recommendation	**(85-100): Exceptional merit and warrants funding, if funds are available**
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: 87

Up to 15 scientific 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.

Mean	87
Median	87
Standard Deviation	2
Highest	90
Lowest	84
Count	15
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	14
Tier 2 (1-84): Not recommended for funding	1

FINAL 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.

Key Strengths and Weaknesses
• The proposed therapy specifically addresses the underlying pathophysiology of the primary cause of the disease. • Therapy addresses the primary cause of the disease. • Strength: First-in-class epigenetic editing therapy targeting the root cause of FSHD through durable DUX4 silencing, supported by compelling mechanistic rationale and a differentiated therapeutic strategy. • Strong scientific plausibility for partial correction because the natural history observation that mosaic FSHD patients with only 30–50% of corrected nuclei show attenuated-to-absent disease provides a biologically grounded rationale for why a partial-transduction gene therapy could still be clinically meaningful. • Strengths: 1) This is a novel, rational, epigenetic editing therapy for FSHD. One-time, transcriptional suppression of the locus, versus a competitor's approach, where repeated administration will be required for post-transcriptional suppression. 2) Over a half dozen patients were already dosed at the time of application. Data available show that 3 have favorable biodistribution (needle biopsies), and 2 have preliminary efficacy readouts. 3) Novel, compact design to fit as payload in AAV. 4) Addressed previous reviewer concerns adequately. 5) Clinical readouts are comprehensive and rational, including whole body MRI and needle biopsies, and assessment of downstream DUX4 target genes. Careful consideration of comparator group from the natural history database. 6) Recruited >50% of target patient population for current open-label trial. • The rationale is supported by robust preclinical data and, more importantly, the availability of initial POC and safety data in the patient population where the initial dose has shown both functional effects and persistence as well as an acceptable safety profile consistent with other AAV-based therapies. • Strong proposal. The team have already dosed over a half dozen patients of approximately a dozen planned for phase 1-2 trial, with the IND cleared only in April of 2025, so fairly rapid enrollment. • Promising data gathered from approximately half of the patients who have already been dosed. • Team was very responsive to concerns raised in earlier submission regarding dosing and cost. • Suppression of a bad gene in a muscular disease. The applicant did a better job addressing dosing concerns than in the original submission. • The applicant has support of major advocacy organizations globally to optimize diverse participant enrollment. • Attractive mechanism of action, one-time IV infusion with a de-risked AAV. High unmet need with a potential to secure high willingness to pay. However, unclear differentiation vs. potential competitor and gap in market entry timing. COGs seem relatively high with CMC risk (e.g., AAV based therapy). • Potential concern about the scalability of their CMC strategy. The proposal could use more depth in terms of CMC description, and how they will scale from small to larger batches of product. • From a CMC and manufacturing reviewer perspective, the manufacturing strategy is good but not outstanding. It is appropriate for a Phase 1/2 systemic AAV program and demonstrates awareness of the key commercialization challenges, but there are several areas where the process still reflects an early clinical-stage manufacturing platform, rather than a fully modern commercial strategy. • Weakness: Long-term safety, durability, immune responses, and commercial accessibility remain significant uncertainties given systemic AAV delivery, high manufacturing costs, and limited human experience. • AAV delivery has inherent biological limits in that it does not transduce satellite cells and only reaches a fraction of muscle fibers — a structural limitation of the delivery mechanism itself rather than something further manufacturing optimization can fully solve. • Great scientific approach was the driving factor; the reviewer believes manufacturing can be achieved at a significantly lower cost with a lower risk profile. • Opportunities for improvement relate to operational planning for recruitment, centralized trial oversight, contingency planning, and participant retention in expansion of the program.
Value Proposition
• Unmet need: FSHD affects an estimated 400,000 to over 1 million people globally, with no approved disease-modifying therapy — current care is purely palliative (physical therapy, surgery, pain management, respiratory support). The US healthcare cost burden is over $12,000 per patient per year above matched controls, translating to $24–60 million annually in California alone.

- There is a high unmet need. FSHD is a rare, disabling neuromuscular disease - reportedly impacting between 16,000 and 38,000 persons in the US. Patients have a poor QoL; ~20% of patients become wheelchair bound by the age of 50. High-cost burden with routine hospital & physical therapy, extensive care coordination and an estimated annual cost of >$28,000 per patient.
- Unmet medical need / competitor landscape: second most common muscular dystrophy in adults; no disease-modifying therapy available.
- This could offer a compelling benefit to patients affected by this severe disease and improve quality of life. It will be of interest to observe how the long-term quality of life is impacted for these patients and the durability of the therapeutic response.
- This is a novel, first-in-class, epigenetic editing treatment for FSHD. Therapeutic strategy for FSHD involves expressing a gene editor under a muscle specific promoter and a D4Z4 guide; all of this is small enough to fit into the vector (single dose IV). The goal is to get this to recognize and methylate the D4Z4 repeat and repress the DUX4 gene, which is abnormally reactivated in FSHD.
- One-time epigenetic gene therapy has the potential to provide durable disease modification and meaningful advantages over chronic RNA-targeting therapies requiring repeated dosing.
- Competitive differentiation — the "one and done" advantage - could add value to the proposed therapy.
- The proposed therapy offers a potential one time disease modifying therapy option for a rare and disabling neuromuscular disorder where none currently exists.
- No other treatments currently available.
- Addresses unmet need with a one time IV treatment offering potential for durable benefit.
- Single dose protocol.
- They have Orphan Drug, Rare Pediatric Disease, and Fast-track designations, plus IND.
- Approximately half of the participants are already dosed in open-label Ph1/2 by March 2026. Dosing of the initial few patients at the lowest dose shows promising results.
- This is a resubmission – and they have addressed previous reviewer comments, as follows: (A) Potential for dose-limiting toxicity: (i) threshold needed is not very high; at least 30-50% perfusion is necessary (below this threshold, mosaic patients are mildly affected); (ii) based on preclinical data a stated range of vg/diploid genome is sufficient for improvement and in the first 3 dosed patients they have a mean vg/dg that is higher (digital PCR, needle muscle biopsy); (iii) Clinical improvement in the majority of the initially dosed patients (low dose), measured versus baseline and versus comparator group (natural history study); various clinical outcome measures, whole body MRI measures, DUX4 target gene correction. (B) Cost of manufacturing: they have made manufacturing changes and estimate considerably lower cost.
- There is now considerable clinical expertise plus patient uptake regarding one-time, IV gene therapy.
- Appreciate the comprehensive safety monitoring plan.
- A reasoned risk-based analysis of clinical uptake has been provided which was informed by surveying the various stakeholders.
- Generally, the proposal is strong from a clinical operations standpoint but there are several risks that will be good to consider.
- Participants will be ineligible for future AAV based therapies, limiting future options, and the immune suppression regimen introduces a complexity that may be difficult for some patients.
- One legitimate competitor in Phase 3 (with Fast Track); Del-Brax (AOC 1020) / Avidity Biosciences; Transferrin receptor monoclonal Ab – conjugated to siRNA for DUX4. So different modality. Another drug (p38 inhibitor) failed in Phase 3.
- There are several therapies being evaluated for FSHD. The most advanced from Avidity Bio - AOC 1020 is in Phase 3 pivotal trial (Fortitude study) - a single IV injection of an Antibody Oligonucleotide Conjugate (AOC) (del-brax) that targets DUX4 mRNA. This product's differentiation vs. AOC 1020 is not fully clear or described. Even if there is mechanistic differentiation, given the long development lead time expected for rare disease clinical trials, and the data needed for long-term follow-up, market entry of this product could potentially erode the unmet need or the competitive edge - unless the clinical data are compelling.
- There is a general investor skepticism around the use of gene therapy for neuromuscular disease (e.g., Sarepta) along with FDA's outlook on CMC/clinical data on AAV-based gene therapies. Alternative approaches e.g., siRNA could be viewed as a more "shiny toy" and increase the proof of burden on this product from a regulatory and investor standpoint.
- The proposed cost per IV injection seems attractive and reasonable (in-line with Elevedys' product for DMD). Will need to see what pricing & reimbursement reforms will occur by 2032+ for one-time therapies. But COGs remain concerning (albeit lowered by 65% which is great). However, will be important to reduce COGs further to sustain commercial viability. As the applicants acknowledge, it will be important to lower the COGs (if the proposed cost per run can achieved, it will be terrific) because, depending upon payer mix, significant rebates and supply discounts will be applied as the product is an IV injection and a

"covered outpatient drug". MediCal and other FFS Medicaid programs will require 23.1% rebate. Plus, hospitals proposed in Phase 1 trial protocol are 340B covered institutions which, upon commercialization, will seek steep 340b price reduction (especially if there is a stiff competition from AOC 1020).

- Strong focus on reducing the cost of the therapy.
- Appears to have a clear unmet medical need. This likely will be a very expensive therapy that will have challenges with the practical uptake and use of the drug. Even with proposed yield improvements at 1000L scale, seems this is insufficient to make the therapy affordable.

Rationale

- Facioscapulohumeral muscular dystrophy (FSHD1, 95% of cases) is postulated to be caused by contraction of the D4Z4 repeat region on chromosome 4q35, which normally keeps the toxic transcription factor DUX4 silenced. When too few repeats remain, DUX4 becomes reactivated in muscle, driving progressive muscle degeneration. The product silences DUX4 without the risks associated with gene editing that breaks DNA strands.
- FSHD is due to contraction of the D4Z4 repeat tract with consequent abnormal reactivation of DUX4, which is toxic to muscles. The therapeutic strategy is rational in down regulating DUX4 expression via epigenetic silencing.
- The proposed therapy specifically addresses the underlying pathophysiology of the primary cause of the disease.
- Strength: Scientific rationale is exceptionally strong, directly linking D4Z4 hypomethylation, aberrant DUX4 expression, disease pathogenesis, and therapeutic epigenetic re-silencing with extensive mechanistic support.
- The product is a single IV injection that aims to durably silence DUX4 gene expression in the muscle cells through enablement of DNA methylation of D4Z4 region of the chromosome. It is using a re-risked, recombinant vector. If therapy works, it could result in reduced muscle cell toxicity and cell apoptosis resulting from DUX4 activity that is typically seen to onset in the teen to 30 years of life leading to a progressive muscle degeneration.
- The rationale is supported by robust preclinical data and, more importantly, the availability of initial proof of concept and safety data in the patient population where the initial dose has shown both functional effects and persistence as well as an acceptable safety profile consistent with other similar gene therapies.
- The nonclinical and on-going clinical data support funding the program.
- The proposed therapy currently has been granted Orphan Drug Designation, Rare Pediatric Designation and Fast Track Designation.
- The system used here is under a muscle-specific promoter, which should help with off-target effects. In the worst case, even if there is leaky expression in other cell types – the normal state of DUX4 in all somatic cells is to be epigenetically silenced.
- It is also compact and conveniently fits into the vector.
- With no reported SAEs, there is clinical support for continued development.
- Clinical output remains limited with no efficacy from ongoing study.
- Weakness: Durability of epigenetic editing in humans and the extent of muscle transduction necessary for sustained clinical benefit remain to be demonstrated in larger clinical studies.
- Long term clinical benefit looks difficult to predict.
- Scientific rationale is sound however the route of administration and capsid may likely drive higher dose, cost, and safety complications. The manufacturing process seems to leverage methodologies such as Triton-X (generally banned in EU) and CsCl purification. Uncertain of how they will optimize this process to significantly bring down costs. May want to focus on newer technologies to drive lower cost. Do not see specification for empty:full ratio, many assays are shown as characterization with report results vs. being a specification.
- Scale up to 1000L seems early and represents a financial risk of loading high cost into a single batch. Previous scale up only to 200L with new process that will go direct into 1000L scale.

Project Plan and Design

- This is a well-designed first-in-human study with appropriate safety monitoring, biomarker strategy, dose escalation, and clinically meaningful functional endpoints integrated throughout the development plan.
- Preclinical data are supportive.
- The program is a resubmission that adds: preliminary data from the first patients dosed, manufacturing yield improvements (tripling the doses per batch, ~65% cost cut, targeting approximately $50,000 /patient

commercially), an increase in trial size, and a triple immunosuppression regimen for the higher-dose cohort.

- The applicant has specifically addressed GWG key concerns from their original application in a timely manner.
- The product already holds Orphan Drug, Rare Pediatric Disease, and Fast Track designations, plus RMAT-adjacent momentum from ongoing FDA correspondence — all of which shorten the runway toward potential accelerated approval.
- The applicant has been provided a clear pathway and expectations by FDA and has designed the relevant project activities necessary to execute a successful clinical development plan.
- Clinical readouts are comprehensive and rational, including downstream DUX4 target genes.
- Whole-body MRI and longitudinal needle biopsies are reasonable readouts for assessment of muscle physiology.
- The clinical trial is already ongoing, with over 50% already dosed. No concern about remaining recruitment.
- Preliminary improvement in phenotype is promising, even in the low dose cohort.
- Multi-center, multinational trial design (5 US, 2 ex-US).
- Limited details for training pharmacy preparation, readiness outside of participating centers.
- Enrollment of the small number of participants may create some difficulty in evaluating cross site consistency, site performance or ability to refine process before later stage studies.
- Recruitment and retention strategies could be more fully developed for population as patient burden is considerable.
- There should be more robust contingency planning and risk mitigation strategies with end to end oversight, vendor management and study governance in more detail.
- In their models, the applicant is assuming launch of the product by 2028 with a conservative estimate of 40 patients treated in year one. This launch timing looks unrealistic. The applicant is asked to confirm updated market entry dates and whether there will be updated assumptions provided.
- Approximately over half a dozen patients dosed, with detailed biodistribution data in approximately half of them, is a thin foundation for a program explicitly aiming toward accelerated approval and NDA submission by 2029 — this is an aggressive commercialization timeline.
- Project plan for manufacture seems aggressive considering the new process has only been scaled to 200L and then will go straight to 1000L GMP manufacture. Unclear why extent of method validation is required at this stage in the absence of clinical data. Do not believe shipping validation and viral clearance study is necessary at this stage.

Project Team and Resources

- The team and resources as presented appear adequate for the program.
- The internal and external resources are appropriate to support the clinical development plan.
- The team has made notable progress since IND clearance in April of 2025.
- Strong and committed team.
- The site PIs at the clinical sites are appropriate, with many KOLs. No concern.
- There is expertise in gene therapy development and clinical neuromuscular research.
- Leadership includes pioneers with significant experience in clinical development.
- Access to the experienced site will strengthen trial execution operationally.
- Remains in need of contingency planning for delays or hurdles unforeseen.
- Expertise remains to be ascertained in this area, but they are working with good partners.
- Highly experienced multidisciplinary team combining CRISPR technology leadership, neuromuscular disease expertise, clinical investigators, CRO support, and regulatory experience. However, there is a major gap in the CMC experience and capability.
- The proposal requests a significant amount of CMC resources to further internalize the development of the process, while stating the selected CDMO's VP, Technical as their expert. This does not seem like a sound strategy and it appears they lack internal CMC depth. Outside of that, the selected vendors are sound choices for their work.

Population Impact

- The proposal has addressed the California population in a very small sample in the Phase 1 clinical trial.
- A comprehensive rational response has been provided that informs access, affordability and expected clinical uptake which is aligned with risk tolerance.

- Unmet medical need; competitor landscape is reasonable.
- Applicant's study considers patients 18 and over. They expect 7-15% market consists of pediatrics with disease onset when child is 5-10 years old; but they make an assumption that children may be eligible based on risk/benefit analysis of adult clinical trials. Avidity's AOC 1020 does not exclude the pediatric group; the applicant will need to establish in all ages to stay competitive.
- They will easily recruit the needed patients in the 7 sites.
- The applicant is a CA-based company; only one US site is in CA.
- One testing center in California other sites elsewhere 12 testing subjects. Not well planned for diversity of participants though the team does utilize advocacy groups. Not in children yet.
- The applicant has support of major advocacy organizations globally to optimize participant enrollment.
- Good connections with the main patient advocacy groups in the US and Australia for recruitment and followup.
- Good PRO collection plan.
- Good patient reimbursement plan.
- Demonstrates an understanding of the clinical burden including QOL, progression and healthcare costs.
- Recognizes differences in severity to better characterize treatment response.
- Limited information for retention plans.
- A potential weakness is that initial eligibility restrictions (including anti-AAV antibody status and early enrollment criteria) may limit access and reduce generalizability until future studies expand to broader patient populations.
- Potential for population impact if cost of goods can be solved. For an application like this, other technologies such as stable cell lines and novel capsids may afford a cost advantage than the current allocation of funds.

Application #	CLIN2-20291
Title (as written by the applicant)	Phase 2 Open-Label Single-Arm Trial of allogeneic CAR T in Participants With Refractory Moderate-to-Severe SLE With Lupus Nephritis
Therapeutic Candidate (as written by the applicant)	iPSC-derived-B cell directed CAR T cell therapy
Indication (as written by the applicant)	Systemic Lupus Erythematosus with Lupus Nephritis
Unmet Medical Need (as written by the applicant)	Potential for renal response and reset of the immune system
Major Proposed Activities (as written by the applicant)	• Completion of clinical site activation and patient enrollment • Clinical Trial Data Monitoring, Database Maintenance, and Data Analysis • Implementation and management of the drug candidate Advisory Board • Community initiatives to enroll underserved SLE patients and improve treatment accessibility • Manufacturing scale-up and registrational readiness of drug candidate production • Manufacture and release of two (2) drug product batches to support the clinical trial.
Statement of Benefit to California (as written by the applicant)	California and its citizens will benefit by the development of an effective treatment option for patients suffering from Systemic Lupus Erythematosus with Lupus Nephritis. The medical unmet need is significant due to the disease's complexity and the limitations of currently approved therapies. This grant also supports the leadership of California as a crucial hub for biotech innovation in the field of regenerative medicines, with the related economic growth opportunities.
Funds Requested	$15,000,000
GWG Recommendation	**(85-100): Exceptional merit and warrants funding, if funds are available**
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: 86

Up to 15 scientific 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.

Mean	86
Median	86
Standard Deviation	4
Highest	93
Lowest	80
Count	14
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	10
Tier 2 (1-84): Not recommended for funding	4

FINAL 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.

Key Strengths and Weaknesses

- Directly addresses an underserved patient population in refractory moderate-to-severe lupus nephritis (LN) patients who have been excluded from most recent drug approval trials which enrolled largely newly diagnosed patients. This program specifically targets patients who have failed ≥2 standard immunosuppressives — a real, unmet gap rather than a "me-too" indication.
- Off-the-shelf manufacturing solves a genuine access problem. Unlike autologous CAR T which requires patient-specific apheresis and manufacturing, limiting scale and adding cost/delay, the therapeutic candidate is derived from a clonal master iPSC line.
- Key Strength - use of an allogeneic iPSC-derived drug product that has been engineered to minimize the risk of GvHD, prevent T-cell exhaustion and enhance CAR T-cell effector function should provide a safer, efficacious approach to treating refractory autoimmune disease.
- Key Strength - Sponsor is an experienced manufacturer of cell therapies, with infrastructure to support the project.
- Key Weakness - CMC plans for assuring that tasks for manufacturing and releasing drug product that will be used to treat pivotal study patients are not sufficiently well defined.
- Of concern, there were multiple FDA comments for CMC that are not reflected in this proposal, including several assay development activities, comparability, and reference standard qualification.
- The key distinguishing attributes of the proposed therapy i.e. reduced/less toxic immunosuppressive pretreatment, allogeneic nature of cells and community based "local" delivery all support a deliberate intent to provide a broader and improved access to therapy to patients who otherwise would not have access.
- Overall a strong application addressing a high unmet need. No LN therapy has been approved in the relapsed/refractory space.
- The primary weakness leading to a reduced final score is the community clinical trial site selection. LN primarily impacts women and communities of color, as was identified in the application. Therefore, having two community sites in a very wealthy neighborhood is unlikely to ensure appropriate patient representation.
- This therapy could potentially be delivered at community sites (vs. tertiary medical centers), offering a value to the larger patient population, especially for those not located near a tertiary center.
- The clinical development plan is well structured and builds appropriately on ongoing phase 1 experience to support a global phase 2 study.
- Strength: The program is supported by RMAT designation, FDA engagement, an established manufacturing process, and emerging clinical safety and activity data in heavily pretreated patients with autoimmune disease.
- Weakness: The proposed potentially registration-enabling study is open-label and single-arm, while candidate-specific efficacy data in lupus nephritis remain limited, creating uncertainty regarding treatment effect, durability, and attribution relative to conditioning and background therapy.
- Validated Target: The target is validated in human systemic autoimmunity by autologous CAR T cell trials, significantly de-risking the therapeutic strategy.
- Logistical and practical advantages: Eliminates the need for apheresis, pre-apheresis immunosuppressant tapering, long manufacturing turnaround times, and may have lower toxicity relative to autologous CAR T cell products.
- High unmet clinical need. Study design uses validated clinical endpoint of Complete Renal Response (CRR).
- Weakness: Limited data confirming that a similar degree of B cell depletion was achieved in the Phase 1 clinical trial relative to autologous CAR T cell approaches.
- This Phase 2 trial addresses a key unmet need in Systemic Lupus Erythematosus (SLE) and the product, if successful, offers significant advantages over autologous CAR T cells. This is grounded on strong rationale, namely deep B cell depletion offers a potential for durable drug free remission and possibly renal recovery. The trial design is well constructed and operations leverage the team's established infrastructure from their phase 1 study.

Value Proposition

- The candidate offers an off-the-shelf, immediately available cell therapy for a severe autoimmune disease population that currently has no adequate treatment option — refractory lupus nephritis patients who have already failed standard immunosuppressive regimens.
- The candidate aims for deep B-cell depletion via a single infusion, offering the possibility of durable disease remission rather than continuous management — fundamentally changing the treatment paradigm for a disease usually managed with lifelong drug regimens.
- Using the B cell target may provide more comprehensive depletion of pathogenic B-cells (where the CAR approach has already shown clinical benefit in B-cell malignancies), dampening/halting the B-cell based autoimmune attack and providing the chance for immune reset/organ recovery.
- Use of an allogeneic iPSC-derived drug product that has been engineered to minimize the risk of GvHD, prevent T-cell exhaustion and enhance CAR T-cell effector function should provide a safer efficacious approach to treating refractory autoimmune disease.
- The possibility exists to provide patients an immune reset, potentially resulting in drug-free remission.
- If a patient goes into remission, the care and cost burdens are reduced overall. The applicant's potential per dose cost would make the therapy attractive to patients, caregivers and healthcare system alike, along with the ability to dose outpatient and use in currently underserved communities.
- The proposed therapy offers the opportunity for a one-time disease modifying therapy with fewer cumulative immunosuppressive toxicity to a SLE population where there is a high unmet need and high progression to end-stage kidney disease.
- An allogeneic platform should allow for an opportunity to improve manufacturing costs.
- The explicit strategy to target community centers vs speciality academic centers should increase access in underserved communities that are disproportionately affected by SLE and patient access.
- There are currently no approved treatments for the refractory disease population of SLE with LN. Therefore, this therapy addresses an unmet medical need. The current drug product candidate would likely be received well by patients, HCPs, and payors as an allogeneic, off the shelf treatment.
- Off-the-shelf allogeneic administration directly removes several access barriers inherent to autologous CAR T (apheresis, mandatory immunosuppression washout with flare risk, multi-week vein-to-vein manufacturing wait).
- Although low COGS is stated, the lack of a suggested price and market access strategy will be an issue with payers moving forward if not addressed in a timely manner.
- The value proposition is based upon the operational advantages, the potential to improve enrollment feasibility, site execution, patient retention, and overall trial efficiency while expanding access to patients who may otherwise be unable to participate in cell therapy studies.
- Strength: Off-the-shelf availability eliminates apheresis and individualized manufacturing, shortens time to treatment, reduces the need for prolonged interruption of immunosuppressive therapy, and may enable broader delivery than autologous CAR T products. The reported manufacturing cost of less than approximately $3,000 per dose further strengthens the potential economic proposition.
- Weakness: Uptake may still be constrained by the need for the lymphodepleting agent, specialized cell-therapy handling, short-term monitoring, infection risk, and uncertainty regarding reimbursement for an intensive therapy in a nonmalignant chronic disease.
- Academic and industry-sponsored trials of autologous CAR T cells for treatment-refractory humoral autoimmunity have established that B cell depletion with this molecular target has the potential to transform patient outcomes in SLE. Assuming this drug candidate can achieve target cell ablation to a degree approaching that of autologous CAR T cells, the therapy is likely to offer a substantial positive impact for patients and the broader health system. The fact that the target is validated in human systemic autoimmunity serves to de-risk the proposal.
- The primary value proposition is that this is an allogenic CAR product developed from iPSC-derived T cells. This allows for centralized manufacture and just-in-time distribution to trial sites. This addresses several of the logistical challenges with autologous CAR products, including: 1) need for apheresis; 2) need to taper immunosuppressants prior to apheresis; 3) prolonged manufacture time and 4) possibly toxicity concerns, allowing for outpatient administration with no required inpatient hospital stay.
- Potential for re-dosing is an advantage, although immunogenicity of product may be a limitation.
- Disadvantages relative to bispecific T cell engagers include manufacturing costs (although substantially lower than autologous cell products) and possibly increased immunogenicity limiting re-dosing. On the other hand, the ability of bispecific T cell engagers to achieve “deep” B cell ablation in human autoimmunity remains unconfirmed.

- Cell therapies are an inherently new therapeutic approach in rheumatology. However, relative to autologous CAR T cell therapies, this approach has an advantage of practicality increasing likely uptake by patients and providers.
- The proposal addresses an unmet need, namely refractory systemic lupus erythematosus with lupus nephritis. Allogeneic CAR T cells to deplete autoimmune B cells holds a major advantage over the many autologous approaches also in development: easier logistics, uniform product quality, lower cost, greater access. Strong potential for durable drug-free remission would have major impact on patients, caregivers, and the healthcare system. Advantages over autologous CAR T cells support greater feasibility and practicality in terms of uptake. Lower risk of insertional mutagenesis due to the insertion locus and clonal nature of iPSC.

Rationale

- Lupus nephritis is driven by pathogenic auto-reactive B cells that infiltrate the kidney and drive inflammation and tissue damage. Standard immunosuppressants broadly suppress immune function without specifically eliminating these auto-reactive B-cell clones, which is why relapse and refractory disease are common. The rationale for this approach is that a target bearing B cell-directed CAR T-cell can achieve deep, comprehensive depletion of the entire B-cell compartment — including the long-lived, tissue-resident auto-reactive clones that drive disease — something conventional B-cell-depleting antibodies (like rituximab) often fail to fully achieve because they do not penetrate tissue niches as effectively as cytotoxic T cells may be able to penetrate.
- Scientific rationale is sound for using a genetically modified iPSC (B cell targeting, reduced risk GvHD) derived T-cell to deplete the pathogenic B-cell population driving the autoimmune response. Lupus nephritis has multiple immunological abnormalities, and B-cells operate in multiple ways to drive autoimmunity.
- Route of administration is intravenous and standard practice for these therapies. Frozen bags of T-cells, though not ideal for community hospital settings without ultra-low temp storage, can be shipped and used globally for this study.
- The regimen is a single dose, as agreed per FDA and the Sponsor in the clinical study design and based upon previous clinical and nonclinical data.
- Supportive clinical data using autologous CAR T therapy against the same target in refractory patients (after lymphodepleting pretreatment), has shown promising results. In a small study, remissions were published to persist in all patients 3 months post treatment.
- Preclinical characterization data demonstrates a pure T-cell product (extra and intra cellular markers) since a single edited clone was used the make the master cell bank and downstream drug product (DP).
- In vitro testing using PBMCs from both healthy and SLE donors showed cytotoxicity toward targeted B cells from both test populations, whilst sparing myeloid and T cells.
- In vivo testing in mice demonstrated an anti-B-cell leukemic effect, lack of toxicity and lack of tumorigenicity. Biodistribution was demonstrated, persistence declined to at or below the limit of detection after approximately six weeks.
- Pre-existing human clinical experience is a strength - the therapeutic candidate is already undergoing clinical study (Phase 1) for B cell-mediated autoimmune disease. Separately, the Sponsor has treated over 50 patients for safety using this approach in B-cell malignancies.
- Strong rationale based on disease biology.
- The broad biodistribution of this therapy aligns with the multi-organ system nature of the disease.
- Available preclinical and initial clinical data in a patient population with B cell mediated autoimmune disease are supportive of safe and active dose recommendations.
- Single dose, IV treatment is standard for cell therapies; the scientific rationale is sound and has supporting clinical study data already.
- The availability of FDA RMAT designation and prior regulatory interactions provide confidence that the proposed study design, endpoints, and operational strategy are aligned with regulatory expectations, reducing development risk.
- Strength: The approach is supported by clinical proof of concept from autologous CAR T studies using the same target in refractory SLE. The CAR T has activity against B cells from healthy and SLE donors, and emerging clinical data with this CAR T show B-cell depletion, disease activity improvements, and a manageable early safety profile.
- Weakness: The approach-specific evidence remains early and heterogeneous across autoimmune indications. Only a small subset of treated participants had lupus nephritis, follow-up is limited, and the contribution of the therapeutic candidate cannot yet be clearly separated from conditioning, background therapy, or natural variability in SLE disease activity.

- Strong justification for the proposed indication. Kidney involvement (lupus nephritis) is a common and organ-threatening manifestation of SLE. Available therapies are incompletely effective in treating inflammation, and remission is not sustained after treatment discontinuation. As an allogenic cell therapy, this candidate offers the potential for sustained disease remission in lupus nephritis without the associated logistical challenges, cost, and (potentially) toxicity risks of autologous CAR T cell products.
- Evidence of disease modifying activity in relevant disease models: no data are provided but in the reviewer's opinion, this is not required. The cellular target has already been validated by ongoing studies of B cell-directed autologous CAR-T cells and by FDA-approved B cell targeting therapies.
- Available clinical trial data: Two completed/ongoing Phase 1 clinical trials of the therapeutic product (over 50 lymphoma patients treated; over a dozen patients with autoimmune diseases treated in a basket trial). A tolerable safety profile is seen in both studies, with no high-grade CRS or ICANS events.
- Limitation (minor): Preclinical in vitro and in vivo murine data supporting the proposal are described in the application. While these are important data, they have limited ability to predict the degree of B cell depletion, including in tissues and secondary lymphoid organs, in human SLE. The proposal states that “rapid and sustained depletion of target-positive B cells” was observed, “consistent with its proposed mechanism of action”. However; these data were not shown, making it challenging to compare with emerging data from trials of autologous CAR T cells directed against the same target.
- Strong rationale based on the known contribution of B cells in SLE and LN pathogenesis. Emerging data of efficacy of CART-based B cell depletion in SLE from multiple groups supports advancement of this candidate. However, provision of data from their Phase 1 study would have been helpful, especially to determine if the depth of B cell depletion (e.g. tissue data, phenotypic re-set) is comparable to that achieved by autologous therapies. The proposal for potential repeat dosing may not be feasible due to immunogenicity. The proposal includes a limited comment on a few patients with malignancy who received repeat doses; only one had an objective response. A phase 1 study of the candidate therapy in SLE has treated at over a dozen patients with SLE across multiple sites - demonstrating feasibility of enrollment, manufacturing, safety.

Project Plan and Design

- The execution timeline targets first patient dosed in July 2026 with dozens of global sites active by March 2027. This is an ambitious multi-country activation pace, particularly for a trial spanning the US, UK, EU, and Brazil simultaneously.
- The applicant is leveraging existing clinical sites for enrollment in this study. They offer that up to 40 global sites may be needed to reach full enrollment, with 10 sites projected as open for enrollment in July 2026 (Enrollment Projection Graph) and all sites open achieved in early 2027. The team has 155-160 people with contractors for support. Enrollment projections over the next ~6 months could be a challenge. The reviewer is not convinced the onboarding rate is feasible.
- The FDA regulatory interactions have been favorable and the Sponsor is taking advantage of regulatory pathways for more certainty in outcomes.
- Collaborative interactions with FDA during the course of clinical development have resulted in clear guidance on regulatory expectations.
- The applicant has secured RMAT designation which allows the opportunity for increased communication during clinical development. Additionally the applicant has been selected to participate in the CDRP program which is also targeted to accelerate clinical development through increasing communications to complete CMC activities.
- In recognition for the small disease population the applicant has increased operational feasibility by broadening inclusion criteria as feasible and planning to opening up to 40 clinical sites.
- The analytical test methodologies appear to remain an area for intense work to meet the FDA requirements for BLA approval. This has been an on-going request from previous FDA interactions and a serious concern for successful product development.
- Process-related impurities methods are not yet developed for MCB, WCB, and/or downstream intermediates testing, as requested by FDA, despite initiating manufacturing for the pivotal study. Analytical comparability is not yet approved or performed to support the current clinical lot being manufactured (a major process change has occurred). The comparability plan must be provided to the agency before initiation, and the reviewer sees no regulatory submissions with the plan yet. Critical quality attributes have not been risk assessed in order to even design the comparability plan. Also the reviewer questions the comparability of the analytical test methods used at each site. The current proposal does not address these concerns. The current proposal asks for funds to support identity testing of raw materials and a software package for materials management and for facility repairs/preparations. However, there are a number of more critical scientific-based studies that are needed to support the success of this program (comparability, impurity assays, potency assay(s), method qualifications during pivotal study, reference standard qualification, etc).

- There are concerns regarding pivotal manufacturing processes, and it is unclear if the scale up process involves a feeder cell line or not.
- There appear to be many FDA CMC comments that were not fully addressed, such as relating to process-related impurities and analytical comparability. This introduces a risk that additional clinical study may be needed, or at least comparability studies, if the clinical trial is performed with material that does not reflect the final product.
- The therapeutic candidate has RMAT designation. Over the course of several interactions/correspondences, the Agency provided clear guidance on analytical and process comparability (facilities, cell banks), assay transfers, potency assurance, stability, and release testing that has to be in place for this clinical study to be leveraged as pivotal. The applicant plans to pool clinical data from different DP batches, including some that incorporate substantial process changes, to support efficacy in the BLA. However, the Manufacturing Plan does not describe the comparability strategy that will be used to demonstrate comparability of the drug product (DP) batches used for treating patients.
- A key bottleneck is the limited size of and manually-intensive manufacturing process for each batch of irradiated cell stock (described as a critical ancillary material). The proposal does not disclose how advanced their implementation solution is for this process (funding is requested for "continuation of scale up studies"), when the solution(s) will be introduced and what impact the solution's results will have on manufacturing and comparability.
- The applicant has drug product inventory on hand for one study and is making inventory for this proposed clinical study. The project plan does not disclose if the inventory currently being produced for the proposed study incorporates all proposed process changes identified by the applicant in discussion with FDA (the manufacturing run is described as post-process lock).
- The applicant has well thought out risk mitigation and financial contingency plans.
- The clinical trial may need a comparator arm, as opposed to only a single-arm design. There also may be risk of enrollment challenges due to other clinical trials that are being conducted in this indication.
- This is an operationally feasible study design that leverages an off-the-shelf product to reduce logistical complexity.
- Enrollment of over refractory LN participants across approximately 40 global sites may be achievable but operationally complex. Competition from approved LN therapies and multiple autologous and allogeneic CAR T programs against the same target could affect recruitment, while site-to-site variability may complicate renal response and safety assessments.
- The target patient population is appropriate and represents an unmet medical need. Outcome measures are standard in the field and have been used to support FDA approval for the treatment of lupus nephritis.
- While the primary clinical complete renal response (CRR) endpoint at week 26 is widely accepted, achieving this predominantly relies on improvement in proteinuria. There is a risk that pre-existing damage in this cohort of treatment-refractory lupus nephritis will limit the proportion of patients capable of achieving CRR, even if the therapeutic candidate exhibits robust impacts on lupus disease activity.
- Feasibility of the proposal is supported by the successful enrollment and treatment of over a dozen patients on the Phase 1 precursor to this Phase 2 study. The study team plans to approach sites that have previously enrolled participants on the Phase 1 study to serve as sites for the proposed trial.
- Enrollment plans: over 50 participants (≥12 to ≤70 years of age). A risk for full enrollment is multiple competing clinical trials for the treatment of refractory lupus nephritis, including several industry sponsored trials of autologous CAR T cells. The prior Phase 1 study of this candidate enrolled over a dozen patients, although this was a basket trial, not limited to lupus nephritis.
- To mitigate enrollment risks, the investigators will approach sites that previously enrolled on the Phase 1 trial. In addition, they will expand to include sites across the globe. The relative ease of candidate administration over autologous CAR T cells is likely to assist with recruitment of sites.
- An interim analysis is planned after ~50% of participants enrolled; no futility analyses are planned in this single arm study.
- Appropriate primary and secondary endpoints and study timepoints. The plan for increasing clinical sites across diverse settings helps ensure timely enrollment and the ability to cover diverse demographics including underserved populations. Genomic analysis of SLE patients is proposed “to further characterize the CAR-T's treatment effect and identify biomarkers associated with response.” SLE-associated/driving mutations should be assessed to determine if particular genetics are associated with a response phenotype; this is not clearly articulated. The proposed conditioning regimen is an advantage in the setting of renal impairment. They will leverage existing framework from ongoing Phase 1, including clinical sites; this supports the feasibility of the trial plan. Impact of pre-existing HLA alloantibodies, especially in the largely female patient population, is not considered.

Project Team and Resources

- The project team and resources are adequate based on successful completion of other clinical trials with the product.
- The applicant has been in this field for a some time and has extensive experience manufacturing clinical materials, with multiple products supplied to various clinical studies. In-house manufacturing assures better process control and eliminates the risks associated with using a CDMO.
- The applicant has added management team members who can support this project. In partnership with their contractors, they should have the knowledge to execute this study. Its unclear whether there is sufficient expertise to chaperone this project through successful BLA submission and approval; therefore, additional specialized resources may be required.
- An experienced internal team with strong external support including a collaboration with Lupus Foundation of America to facilitate clinical trial enrollment.
- Experienced team in clinical development, perhaps naive for commercial readiness.
- Existing operational experience from related trials reduces execution risk for study startup, supply management, safety oversight, and multi-center trial conduct.
- The leadership team is well suited to complete the project. The trial will be led by a board-certified rheumatologist and a senior individual with clinical operations and biometrics expertise. This complementary expertise will increase the likelihood of trial success.
- The plans for study coordination and execution were outlined in the proposal. Planned consultants and subcontractors have been identified.
- Data management: the study will use CRFs developed for the prior trial. The study will also use the same EDC system, reducing the need to build new data management tools.
- Manufacturing will be performed in house at the applicant's manufacturing facilities.
- An external advisory board is planned.
- The team is led by a rheumatologist who has led the Phase 1 trial. Inclusion of oncologists in the trial is a plus, and manufacturing resources already in place.

Population Impact

- Since the trial specifically targets the refractory subset of the LN population, the addressable patient pool for the therapy in California would be a fraction of the LN total population. The proposal does not quantify that refractory percentage numerically, stating that "a significant proportion" of LN patients experience inadequate response, relapse, or treatment-limiting toxicity.
- The applicant appears to understand the target indication, disease burden, care and health outcomes. They have already used the product in the Phase 2 target population as part of the Phase 1 study.
- Refractory or relapsed SLE LN patients have limited options and other, similar cell therapies are primarily autologous, with different difficulties in delivering treatment. An allogeneic, optimized CAR T-cell product that is “treatment ready” for B-cell depletion in patients that don’t respond to prior therapy is a sound approach.
- The key distinguishing attributes of the proposed therapy, i.e. reduced/less toxic immunosuppressive pretreatment, the allogeneic nature of cells and community based "local" delivery, all support a deliberate intent to provide a broader and improved access to therapy to patients who otherwise would not have access.
- As previously, the primary weakness leading to a reduced final score is the community clinical trial site selection. LN primarily impacts women and communities of color, as was identified in the application. Therefore having two community sites in a very wealthy neighborhood is unlikely to ensure appropriate patient representation.
- The patient recruitment material for outreach needs to be altered and made more simplistic to account for various socioeconomic patient populations.
- By reducing logistical burden and supporting broader site participation, the study has the potential to improve enrollment while increasing the generalizability of trial results.
- The off-the-shelf platform may meaningfully reduce access barriers associated with autologous CAR-T therapy, including apheresis, manufacturing delays, prolonged treatment interruption, travel, hospitalization, and the risk of patient-specific manufacturing failure.
- The proposal appropriately addresses known demographic disparities in lupus prevalence and proposes strategies to enroll underserved populations. They will also open international sites in order to study the breadth of at-risk groups.
- Expanding the planned study population to include adolescents is a strength.

- The study team plans to approach community sites to increase access to this cell therapy. Opening study sites in community centers is likely more feasible with an allogenic cell product vs. autologous CAR T cells.
- The proposal indicates an understanding of the population in need.
- Appropriate timing of treatment in the context of disease course. Plan for subject distribution is well considered and includes contingency plans if enrollment challenges are encountered.

Application #	CLIN2-20409
Title (as written by the applicant)	An RNA Splicing and Base Editing Inhibitor to Target Cancer Stem Cells in Refractory Myeloid Malignancies
Therapeutic Candidate (as written by the applicant)	As a genetic therapy, the drug candidate is a small molecule RNA splicing inhibitor that prevents ADAR1p150-mediated therapeutic resistance in HR-MF and sAML.
Indication (as written by the applicant)	Refractory high-risk myelofibrosis (HR-MF) and secondary acute myeloid leukemia (sAML) are the target indications for the Phase 1 trial.
Unmet Medical Need (as written by the applicant)	The candidate addresses an unmet need for high- risk myelofibrosis and AML patients, who a have an average life expectancy of less than 18 months, often as a result of ADAR1-activated CSC propagation and ineligibility for hematopoietic cell transplantation based on comorbidities or advanced age.
Major Proposed Activities (as written by the applicant)	• With CLIN1 funded DP development, 4,000 vials of i.v. drug candidate are available for the trial. • Enroll 28 patients in Phase 1 trial to assess safety and early efficacy in ADAR1-activated CSCs. • Identify splice isoform and RNA editing biomarkers of drug candidate response in trial participants. • Identify maximally tolerated dose (MTD) of drug candidate. • Identify dose limiting toxicity (DLT) of drug candidate. • Establish recommended phase 2 dose (RP2D) with splice isoform and ADAR1p150 RNA editing biomarkers.
Statement of Benefit to California (as written by the applicant)	The Phase 1 safety and ADAR1p150-activated cancer stem cell biomarker identification trial of our drug candidate would benefit the State of California by addressing the high unmet medical need for effective therapy for patients with high-risk myelofibrosis and secondary acute myeloid leukemia who typically have a less than 18 month life expectancy as a result of being refractory to standard therapies or ineligible for hematopoietic cell transplantation due to co-morbidities and advanced age.
Funds Requested	$5,546,253
GWG Recommendation	**(85-100): Exceptional merit and warrants funding, if funds are available**
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: 85

Up to 15 scientific 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.

Mean	87
Median	85
Standard Deviation	2
Highest	92
Lowest	85
Count	15
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	15
Tier 2 (1-84): Not recommended for funding	0

FINAL 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.

Key Strengths and Weaknesses

- The mechanism builds on a cover-story paper in a high-profile journal from the same scientific team, with a specific and testable hypothesis (ADAR1p150 drives cancer stem cell self-renewal across 20+ cancer types) rather than a novel, unvalidated concept.
- The product appears to have a very short half-life — as low as roughly 7 minutes in some preclinical species, raising legitimate questions about whether twice-weekly IV dosing can sustain meaningful target engagement — especially notable given that earlier spliceosome-targeting drugs in this same class failed clinically due to stability and tolerability problems.
- A splicing inhibitor that has anti leukemic effects.
- This therapy, if successful, has the potential to treat refractory cancers.
- The investigators do not address how they will support a sample of primarily older adults. No provisions are made in the budget for housing, travel, and caregiver support that will be needed to recruit and retain older adults in a study with an intense treatment schedule.
- The information on the DSMB is not detailed enough to determine how the Board will function as an independent entity to adjudicate adverse events.
- Applicants have a cleared IND, and a CMO and CRO lined up. They are also self-funding approximately 30% of the costs themselves and received prior CIRM funding, demonstrating prior promise.
- Applicants should consider the independence of the DSMB and how review of SAEs will be handled to ensure independence.
- A well-prepared operational plan with relatively low execution risk for a Phase 1 study.
- The role of ADAR1 and its alternative splicing in CSCs has been well studied by the group. The drug has been carefully developed through previous CIRM funding. Both refractory high-risk myelofibrosis (HR-MF) and secondary acute myeloid leukemia (sAML) are clinical groups in need of novel therapies.
- From a regulatory perspective, the key strength is that the drug candidate has a favorable safety and efficacy profile, as demonstrated in completed CIRM TRAN1 and CLIN1 funded pre-IND and IND enabling studies.
- Strengths include, 1) First-in-class ADAR1p150 splicing inhibitor targeting cancer stem cell biology with a differentiated mechanism, supported by an FDA-cleared IND and substantial preclinical development. 2) Strong translational package integrating pharmacology, biomarker strategy, manufacturing readiness, and experienced academic oncology sites, increasing feasibility of trial execution.
- Weakness: Clinical benefit remains unproven in humans; the proposed value proposition relies heavily on preclinical evidence and mechanistic rationale rather than early clinical efficacy data.
- Strong scientific rationale, pre-clinical data, and justification for moving into the clinic. The number of doses they will evaluate in the dose escalation portion of the study seems excessive.

Value Proposition

- The proposed indications for the interventional treatment for HR-MF and sAML are justified because these populations have the shortest survival among hematologic malignancies (<18 months). Most patients are ineligible for HCT due to age and co-morbidities, and no standard therapy achieves durable, complete, treatment-free responses.
- The currently available treatments for relapsed/refractory sAML and HR-MF are associated with significant toxicity and/or low efficacy. The candidate therapy's stereochemical modification provides greater stability and potency, and removal of the a specific moiety reduces off-target interactions. It is also spliceosome mutation-independent, meaning it works regardless of whether the patient carries SF3B1, SRSF2, U2AF1, or ZRSR2 mutations.
- If the product proves safe and efficacious, the study indications could be expanded to other ADAR1p150 overexpressing cancers.

- The population being studied is very specific. Payers can use trial inclusion/exclusion criteria in their coverage policies to only cover to that population studied and not the full indication statement. Applicants should be aware of that as they approach Phase 2 and 3.
- Despite what people may think of payers, overall survival (OS) would be the most important endpoint they want to see. A 3-month improvement may be considered good if you show that this same population that you studied currently achieves 6 or so months of survival typically. If mOS is 5 years, they likely won't see much value. Would need other improvements along with it. Objective response rate (ORR) would be good as well, but payers will ask about survival due to severity of disease and how the disease is described to them by field team. Safety looks good, but payers typically do not base decisions off this.
- In oncology, National Comprehensive Cancer Network (NCCN) guidelines (category 2a or better) in the US are very important to include to secure favorable access. These guidelines should be very high priority.
- Dosing: Due to IV administration, there is another access and pricing stakeholder to consider (in additional to traditional payers like Commercial, Medicaid, and Medicare) when evaluating potential hospital protocol decision makers.
- A reviewer appreciates the pricing approach's plan to reflect the candidate's efficacy, safety, and convenience compared to existing treatments. One could get a good idea of pricing based off the analogs/competitors that are identified and should do so. Also, the team should look at how some commercial and Medicaid plans cover these products based off their price. Danyelza is not an appropriate comparator to use. I also think <$100,000 under values the product. More work can be done here using existing public information.
- A well thought out plan for bad diseases that's feasible at multicenter sites and provides a good patient access strategy.
- This study addresses an unmet medical need for patients with secondary AML and MF.
- Current treatments are somewhat effective but are associated with relatively high patient burden and health care costs.
- From an operational perspective, this approach is compatible with standard oncology infusion practices.
- The agent is proposed to target LSCs that may improve long-term outcomes.
    - Treatments for HR-MF and sAML are needed for relapsed and refractory patients.
- From a potential benefit perspective, this approach likely has the common mechanism of inhibition splicing mediated activation of ADAR1 in as many as 20 cancers that share this pathway of therapeutic escape.
- Addresses a major unmet need in refractory HR-MF and sAML, where existing therapies produce poor long-term outcomes and many patients are not transplant candidates.
- Interesting potential for impact into HR-ME and sAML, but potentially also into other settings where the impact of this molecule could potentially be significant.

Rationale

- This synthetic small molecule inhibits malignant ADAR1p150-mediated RNA splicing and editing, which drives cancer stem cell (CSC) self-renewal, therapeutic resistance, and immune evasion. It selectively targets CSCs while sparing normal hematopoietic stem and progenitor cells (HSPCs).
- The nonclinical studies support the safety and efficacy of the product.
- Route and timing of the infusion are justified in the application.
- There is good nonclinical data to support this project. There is also some data that this compound could be effective against other indications, although that is not pursued in this proposal. However, the plan to evaluate biomarkers as part of this plan could inform the design of later trials.
- Includes a conventional dose-escalation design with clearly defined safety, PK/PD, and efficacy endpoints, providing an operationally sound framework for early clinical development.
- The investigators have demonstrated that aberrant ADAR1 isoforms are required by CSCs in many diseases, and the preclinical data in myeloid malignancies are robust. The current project directly arises from previous CIRM funding.
- The candidate is the first ADAR1 inhibitor with an active IND with the potential to inhibit immune evasion, malignant regeneration, and therapeutic resistance in 20 different malignancies.
- The candidate has a favorable safety and efficacy profile, as demonstrated in completed CIRM TRAN1 and CLIN1 funded pre-IND and IND enabling studies.
- Extensive preclinical evidence includes disease-relevant human models, pharmacology, toxicology, biomarker development, RNA sequencing, and translational assays supporting progression into first-in-human testing.

Project Plan and Design
• The proposed clinical trial appears to be feasible based upon the clinical sites and the eligibility criteria applied for these patients. • A standard phase 1 clinical trial. • The proposal follows a conventional and well-established early-phase oncology design with clearly defined dose-escalation rules, safety monitoring, assessments, and stopping criteria. • The clinical trial is well designed, and patient availability is enhanced by the inclusion of multiple clinical sites. The correlative studies are meaningful. • Based on biological rationale and preclinical activity, the proposed phase 1 clinical trial is designed to evaluate the safety and early efficacy of the candidate for the treatment of patients with HF-MF and sAML. The trial will generate clinical data to support this evaluation and to support go/no-go decision making for further product development. • Enrollment may be constrained by the rarity and advanced disease status of the target population, while the staggered dose-escalation design could slow study completion despite mitigation plans. • Strong plan, team, budget, and timeline.
Project Team and Resources
• The applicant team and the contracted organizations appear to be adequate to conduct the program successfully. • The team need to allocate more for commercialization, access and affordability; it is very light currently. • A good team set up for success. • Three Alpha Clinics will be used to support this phase 1 study. • They have a CMO and CRO lined up, with a cleared IND. The team is well-thought out and budget seems appropriate. • Suggest the team clarify the independence of the DSMB and how SAE reviews will be performed. • Have completed CIRM-funded preclinical and IND-enabling studies that resulted in an active FDA IND. Experienced hematologic malignancy investigators, providing infrastructure needed to support execution of a complex first-in-human oncology study. • The proposed team is well suited to carry out the proposed clinical trial. • The project team consists of managers at the sponsor institution, at the clinical sites, and at the clinical CRO. The team appears to be experienced and appropriate for the proposed product development. • The resources at the manufacturing, CRO and CMOs seem to be sufficient to achieve the project goals in compliance with FDA requirements. • Leadership combines internationally recognized scientific expertise in ADAR1 biology with experienced clinical investigators, established cancer centers, and specialized CRO partnerships. • The selection of team members, FTEs, clinical CRO, and 3 Alpha Clinics are appropriate for this trial and a strong point showing the applicant's understanding of the space.
Population Impact
• The study population appears to be appropriate based on the incidence of the target indications. • Eighty percent of the sample will be 65 years of age and older. • Given the intensity of the drug administration schedule and the anticipated age of the sample (primarily older adults), no funding is allocated for patient and caregiver transportation and lodging. In addition, no plan is explicated for how elderly and likely sick patients will be accommodated in this trial. This lack of budgetary consideration will influence recruitment and retention of study participants. • The population is older, with 80% 65 or older, and 40% 85 or older. This could prevent challenges with need for caregivers, transportation, etc. It is also an intense dosing regimen which could introduce challenges. • The multisite approach including the use of CIRM Alpha Clinics is a positive. Participation support for the older impacted patient population is not well described. There is a potential lack of needed patient support to participate in the trial. • While AML rates are provided, rates of secondary AML and MF are not provided in the proposal. • The targeted conditions are more common in men, so 60% of the study sample will be men. • The estimated ethnic distribution is 40% Hispanic or Latino, 13% Asian, 6% Black or African American, and 40% White.

- While the application states that a DSMB will be established, details are lacking on the composition of the board and how it will perform an independent adjudication of the adverse effects associated with this trial.
- Enrollment may be slower than in more common hematologic malignancies, requiring experienced investigative sites with access to these patient populations.
- Further consideration of care and feasibility of an older population of patients should be provided.
- The potential impact on the intended cancer population will be to increase effectiveness across a broad range of cancers that are driven by cancer stem cells. The proposed product may also decrease morbidity associated with the competitor products.
- Targets populations with extremely poor prognoses, limited therapeutic options, and substantial healthcare burden, providing potential for meaningful clinical impact if successful.
- The therapeutic approach holds potential for significant impact within sAML and HR-MF and beyond in other tumor types.

Application #	CLIN2-20350
Title (as written by the applicant)	Optogenetic Therapy for Treatment of Stargardt Disease
Therapeutic Candidate (as written by the applicant)	Optogenetic gene therapy for patients with Stargardt disease
Indication (as written by the applicant)	Stargardt disease
Unmet Medical Need (as written by the applicant)	The candidate gene therapy will treat patients with advanced Stargardt disease (STGD) who currently have no other approved treatments.
Major Proposed Activities (as written by the applicant)	• Potency assay developed • Complete enrollment of 9 patients and 3 months follow-up on all patients • ddPCR assay validated • One GMP lot to support later-phase clinical development released • Submission of 12 month follow-up trial results to regulatory agency
Statement of Benefit to California (as written by the applicant)	Stargardt disease (STGD) is a progressively debilitating disease which leads to blindness. Of the approximate 4000 patients living with STGD in California, many have advanced disease, to the point of total loss of visual acuity. Most of these patients need to receive healthcare benefits, special living assistance, and suffer from loss of financial independence. This candidate therapy represents a potential breakthrough treatment for a high unmet medical need to improve their quality of life.
Funds Requested	$7,935,162
GWG Recommendation	**(85-100): Exceptional merit and warrants funding, if funds are available**
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: 85

Up to 15 scientific 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.

Mean	87
Median	85
Standard Deviation	3
Highest	95
Lowest	85
Count	13
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	13
Tier 2 (1-84): Not recommended for funding	0

FINAL 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.

Key Strengths and Weaknesses
• Strength: The applicant has illustrated the unmet need for additional treatments in Stargardt Disease (SD), particularly those that can restore vision in a genotype-agnostic patient population. Although there are multiple products in the pipeline for SD, there seems to be room in the market for multiple treatments, particularly if the clinical data are strong. • Strength: The applicant noted the challenges with the gene therapies and a single administration, both with up-front costs and existing infrastructure issues. The applicant is not in denial of the challenges and recognizes that they need to be addressed. • This therapy offers the potential of a single life-long dose, which also could be delivered in patients who are already experiencing severe vision loss. This offers a compelling value proposition. • Overall, this is an innovative and potentially transformative proposal addressing a population with advanced Stargardt disease for whom disease-modifying approaches are unlikely to restore lost vision. The genotype-independent, intravitreal optogenetic strategy is differentiated, minimally invasive, and supported by compelling animal efficacy, ocular safety data, an active IND, and relevant clinical read-through from their prior candidate. • Project demonstrates realistic operational planning and patient engagement. • Key strengths from a regulatory perspective: The regulatory plans for FDA engagement and the prior FDA interactions are all reasonable and sound. The intended application for RMAT, FastTrack, and Orphan designation are strengths for the plan. The good progress of the IND to date will support these applications and is a definite strength. • Key weakness from a regulatory perspective: The plans for potency assay development suitable for a Phase 2 trial are reasonable but depend on development of a novel cell line that can support cell-specific transcription and demonstrate functionality of the selected transgene. The timeline for such development is uncertain, and technical difficulties could result in delays for Phase 3product development in terms of potency assay validation and FDA acceptance. • Strengths: If successful, this approach has potential to restore vision in patients with late-stage Stargardt macular dystrophy. Simple delivery method can be an in-office procedure. One-off treatment. Targeting ON-BP cells with an ON-BP-specific promoter has potential to restore high-quality vision. • Weaknesses: Other competitive therapies are in development including optogenetic and gene therapy products. Whether this one has a clear, competitive advantage to become successful is not clear based on the data to date. Preclinical data do not include models of retinal degeneration, so whether this therapy has effect in a degeneration state remains to be seen. The funding requested, including the size of the team, seems disproportionately high for the size of this FIH, less than ten patient study. • The approach is novel with transduction of an optogenetic protein to the targeted ON-bipolar cells of the retina to restore vision in patient with Stargardt disease. There is preliminary proof of concept in humans from a similar AAV delivering the same optogenetic protein under the control of a different promoter. The CMC is well established with IND clearance and a reasonable plan for the current clinical phase and a gated approach to investment for future phases. • Weakness: The applicant has started the market access landscape assessment as required; however, it was not completed (noted as "in progress" on Slide 5). Only a few slides exist in the materials provided that address the size of the market, potential customers, and unmet needs; many details are missing. Although the applicant has done the work for other disease states, the applicant has not completed the work for SD.
Value Proposition
• The candidate therapy aims to be the first optogenetic medicine for Stargardt disease — restoring vision via a single, in-office intravitreal injection, regardless of a patient's underlying ABCA4/ELOVL4/PROM1 genotype. Because it acts on surviving ON-bipolar cells rather than the degenerated photoreceptors themselves, it could help the roughly 50% of Stargardt patients with advanced disease who are ineligible for gene-replacement or neuroprotective approaches that require intact photoreceptors. • The applicant noted that additional research is needed to evaluate the feasibility and practicality of the therapy's uptake by patients, providers, and payers, and this will occur if the grant is awarded. • The revised statement makes it clear that though the therapy does not correct the underlying genetic defect, it does aim to restore functionally meaningful vision supporting independence and mobility. It claims to be supportive and complementary rather than competitive with other approaches.

- This treatment, after passing through all of the safety and FDA tests, will significantly improve the life quality of patients and their caregivers.
- The plan is designed in such a way that the uptake and feasibility seem likely to succeed. The one time injection at convenient sites with a large eligible population make the study seem realistic. The follow up period may be more challenging, but they have designed plans for dealing with that. Therefore, if safe, seems very practical.
- There is a strong value from an implementation perspective as the therapeutic approach would minimize the need for specialized infrastructure or extensive provider training. As there are no approved therapies for Stargardt disease, it would be favored if safety and efficacy are demonstrated. Reduction of logistical barriers for patients and caregivers support protocol compliance and data quality.
- FDA recognized the potential for clinical benefit for the closely related predecessor product. The applicant plans to submit RMAT and Fast Track Stargardt disease and has good prospects of receiving these designations due to unmet treatment needs in the Stargardt population
- A genotype-independent, one-time intravitreal treatment could serve patients across ABCA4, ELOVL4, PROM1, and genetically unresolved disease, while avoiding the need for mutation-specific products, retinal surgery, or external light-amplifying goggles.
- Value Proposition: Strong. The candidate therapy offers a compelling value proposition, with potential to restore vision in patients with late-stage Stargardt macular dystrophy. Clinical outcome: First optogenetic medicine for Stargardt Disease; potential to restore high-resolution vision regardless of genetic subtype — no current benchmark (competitors are in clinical trials). Patient/system impact: Meaningful quality-of-life gains (acuity, reading, facial recognition) with a single lifelong dose, reducing burden on patients, caregivers, and the healthcare system. Feasibility: Simple, in-office delivery and shorter follow-up support easy adoption by providers and better access, including for underserved communities.
- There is unmet need for Stargardt Disease, and the proposed approach is innovative and has preliminary data supporting its use.

Rationale

- The treatment rationale is reasonable while novel. Harnessing unaffected neural cells that can replace functionality of light sensing and neural signal transduction in place of affected cells in the intra-ocular space is well-supported by the preclinical data.
- The proposal seems well supported by the scientific evidence.
- The rationale for targeting preserved ON-bipolar cells in advanced retinal degeneration is biologically sound. These cells remain present after photoreceptor loss and retain connections with downstream retinal ganglion cells, creating an appropriate substrate for optogenetic vision restoration.
- There is overall limited preclinical safety data. However, the scientific rationale is sound.
- The pre-work done has been quite compelling.
- The proposed Phase 1 is consistent with the current stage of development and appropriate for a FIH gene therapy study. Collecting preliminary efficacy data early in development has the potential to inform dose selection and support subsequent clinical development decisions. However, there is limited information about the underlying MOA and limited operational evidence supporting disease-modifying activity. Limited supportive data for durability of effect, but with the gene-independent approach and unmet need, there is a compelling interest in continued clinical development.
- This reviewer supports the scientific rationale — targeting bipolar cells for macular dystrophy, rather than retinal ganglion cells as in the applicant's retinitis pigmentosa and choroideremia programs, offers greater potential for higher-acuity vision. Previous critique: does not correct underlying defect — but that is acceptable. This is a vision restorative approach. Macular targeting in pan-retinal disease is also acceptable. Good preclinical data in TKO model and sound choice of therapeutic vector composition includig: AAV capsid, the selected promoter, and the optogene with improved light sensitivity. The TKO model, however, is not a model of retinal degeneration, and no data are shown in these models. Toxicology and biodistribution data in relevant preclinical models show no safety issues.
- From a CMC perspective, the proposed vector is well designed, appears to deliver to the appropriate cells and has a well documented manufacturing approach.
- The rationale and especially the route of administration seem compelling.

Project Plan and Design

- The team has put together a clear outline of the go or not-go decisions for the plan related to the safety concerns with the small initial cohort of patients. The applicants have carefully outlined the enrollment goal, and the partners they will use to achieve them. The manufacturing and analysis protocols are clear and feasible.
- The risks and plans to deal with those risks are clearly laid out.

- The project plan is well designed from a CMC perspective and has received IND clearance. The approach for CMC preparation upon the success of the Phase 1 trial is appropriate, and the decision gates that have been added make sense.
- Their IND was cleared within 1 month, indicating there were minimal issues with their submission.
- The trial protocol seems feasible and well-designed, with independent central reading.
- The protocol seems feasible both operationally and clinically. It is well designed for a FIH Phase 1 that will also generate preliminary efficacy to support decisions for next steps. The independent central read is a strength that with standard efficacy assessments will improve data consistency. The prophylactic steroid regimen flexibility of distribution also reduces any kind of delay or inconsistency.
- The manufacturing process, the in-process and lot release criteria, stability program, and QC plans are all appropriate for Phase 1 and 2 trials, and the applicant understands the basics for BLA application. The project plan and design will support further go/no-go decision making.
- The project includes the necessary clinical, bioanalytical, regulatory, quality, endpoint-assessment, genetic counseling, patient-support, and manufacturing activities required to complete the trial and prepare the program for subsequent development.
- Study design is reasonable. Small Phase 1 study, 3 dose cohorts. 12-month follow-up. DSMC after each cohort. 3 US sites. It is unclear whether these are the same as the applicant's related product sites. It is unclear whether resources are therefore fully justified; for a 9-patient trial, perhaps a bit in excess. Given that the applicant already has experience with a related product, it is unclear why doses are different here (starting with much lower). The applicant states efficacy results are promising for the related product, but no detail is provided. Single intravitreal injection. Sound follow-up. Primary outcome is safety. The applicant will test appropriate efficacy endpoints and has an ongoing natural history study informing this interventional trial. Manufacturing process seems appropriate. This reviewer assumes a similar process would have been in place for the related product.
- Without a validated, functional potency assay, there is a regulatory risk that the data collected in the clinical trial may not be adequate for a BLA approval.
- This reviewer thinks the applicant could have done more work to complete the requirements for the market landscape assessment, particularly as the applicant has this work completed for other disease states. However, due to the unmet need and clinical potential of the product, this reviewer did not want to take the applicant out of the running completely. This reviewer is keeping the recommendation at 85 points.

Project Team and Resources

- The project team is well prepared and experienced with demonstrated prior success for the related product. Both the related product and the current product follow complex but largely identical manufacturing and characterization processes.
- The reviewers have recognized the strength of this team; in fact, the questions were centered on whether such a stellar team was required for this phase of the effort. The applicant's response is that because of the safety risks for this first in human effort, a robust team is required.
- The applicant is working with a reputable CDMO, which is reassuring for product manufacturing.
- The operations team leadership with more than 20 years of focused experience in both clinical development as well as ophthalmology, along with the appropriate allocation of oversight for the other activities, appears to be a well-qualified leadership team. There are also appropriate subject matter expert vendors that will support study conduct, and the DSMC provides appropriate safety oversight. There will need to be additional details provided for communication pathways, governance, decision-making process, and end-to-end oversight to ensure efficient coordination across sites and vendors. With the additional details for oversight and communication and organizational coordination, including defined roles for tactical operations, it would support the overall team and resource confidence.
- The team and the resources appear adequate to achieve the goals of the proposed program.
- The team is appropriate.
- The project brings together expertise in retinal optogenetics, inherited retinal disease, ocular gene therapy, clinical ophthalmology, imaging, visual-function testing, regulatory strategy, and AAV manufacturing. The team also has directly relevant execution experience from the related product clinical program.
- Team has appropriate experience and expertise. This reviewer agrees with previous comments in the initial application that it is extensive. Not changed for this submission. Justification given that it is needed for this first-in-human trial: "The composition of the team reflects the requirements of a first-in-human, IND-active gene therapy program, which necessitates rigorous oversight across clinical operations, safety monitoring, CMC, regulatory compliance, and quality management." It is unclear whether the team is

already in place for the applicant's related product. It is unclear whether any timelines are done in parallel.

- The application appears to request a good bit of funding to support future phase 2-3 trials. It may be more appropriate to provide funding in a staged approach.
- The applicant seems to have a contractor identified for conducting future pricing, reimbursement, and market access issues as the applicant has used this consultant for previous work. This reviewer would suggest bidding out this work to multiple vendors to have an array of project options and pricing for future work.

Population Impact

- The applicant has a very clear understanding of the ethnic and cultural differences associated with detection, diagnosis, and treatment of Stargardt disease.
- The outreach and engagement plans and the diverse sites support the outreach and engagement strategies the applicant proposes. The feasibility is enhanced by the fact that the sites are long-term partners with this team in a variety of similar projects. The group of sites appear to know what the applicant is doing.
- There is a good understanding of the recruitment challenges, and there is an appropriate strategy for the target population along with experienced sites and links to patient access groups. The adaptive strategies for enrollment support achievable projections. While feasible to reach enrollment goals, it would be good to have additional efforts to more diverse communities for stronger demographic representation.
- The RMAT approval of the predecessor product demonstrates that FDA recognizes ocular diseases as serious and agreed that the preliminary clinical evidence showed potential for addressing an unmet medical need. It is likely that this candidate will meet this standard for RMAT approval. This is a strength of the proposal from the regulatory perspective.
- The genotype-independent approach could ultimately benefit a broader advanced Stargardt population than mutation-specific gene therapies and avoids excluding patients with rare causal genes or inconclusive genetic testing.
- The applicant demonstrates awareness that Stargardt disease presents variably across the affected population, including differences in age of onset, diagnostic pathway, and disease burden, while noting that most cases converge on a similar clinical phenotype regardless of underlying genetic cause. The genotype-independent design is well justified — although ABCA4 mutations account for the majority of cases, a clinically meaningful subset of patients have other rare pathogenic variants (e.g., ELOVL4, PROM1) or inconclusive genetic diagnoses despite a classic Stargardt phenotype; restricting enrollment to ABCA4-confirmed patients would exclude a population with similar clinical presentation and equal unmet need. Eligibility is restricted to patients with a consistent level of advanced vision loss and confirmed preservation of inner retinal architecture, keeping the study population biologically appropriate and clinically comparable.
- Appropriate given the rare disease.
- With such a small starting sample, gauging the demographics is difficult. This reviewer was surprised that the Latino target was set low given the demographics of California and the sites, but though the applicant expects certain numbers for gender and race, the applicant will take who can be enrolled for those qualifying over 16 for the study.
- Again, given the small sample size and the difficulties of recruitment, the goals seem appropriate and the exclusions (such as women who are or may become pregnant) are related to safety issues.

Application #	CLIN2-20389
Title (as written by the applicant)	Phase I Clinical Trial of a Trispecific CAR T-Cell Therapy for Multi-Antigen Targeting in CNS and B-Cell Lymphomas
Therapeutic Candidate (as written by the applicant)	A cell therapy using a patient's own immune cells, engineered to find and destroy CNS and B-cell lymphomas.
Indication (as written by the applicant)	Treatment of aggressive CNS and B-cell lymphomas that have not responded to standard therapies.
Unmet Medical Need (as written by the applicant)	CAR T therapy has the potential to provide curative therapy for CNS lymphoma but remains excluded in the majority of trials. Inclusion of CNS lymphoma must be prioritized in clinical trials to provide potentially curative treatment for these patients with limited therapy options.
Major Proposed Activities (as written by the applicant)	• Trial activation and enrollment launch • Tri.CAR T-cell manufacturing and QA • Dose escalation phase (3+3 design) • Recommended phase 2 dose expansion cohort • Exploratory immune monitoring and biomarker analysis • Final data analysis, clinical study report (CSR) preparation, and regulatory follow-up
Statement of Benefit to California (as written by the applicant)	This research will create high-quality jobs, advance scientific innovation, and expand clinical trial access within California. It supports in-state manufacturing, strengthens California's leadership in cell therapy, and provides new hope for patients with limited treatment options, all while ensuring taxpayer-funded benefits stay local.
Funds Requested	$14,999,558
GWG Recommendation	**(1-84): Not recommended for 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: 84

Up to 15 scientific 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.

Mean	83
Median	84
Standard Deviation	2
Highest	85
Lowest	80
Count	14
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	3
Tier 2 (1-84): Not recommended for funding	11

FINAL 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.

Key Strengths and Weaknesses

- Addresses a well-documented, clinically significant problem (antigen-escape relapse) with a scientifically grounded strategy, backed by supportive preclinical literature on the trispecific approach.
- CMC remains an issue.
- Lower projected per-patient manufacturing cost than commercial CAR-T products potentially improve cost-effectiveness if efficacy is proven.
- Key Strength - the TriCAR targets three antigens using a design that includes two co-stimulatory domains. The construct is designed to prevent tumor escape, provide broader tumor recognition and enhance persistence.
- Key Weakness - CMC plan allows for up to 4 drug product configurations (8- or 12-day culture/fresh or frozen), describes NIH as a parallel manufacturing site and plans to include one or more Point of manufacturing and Care sites for patient product manufacturing and treatment. Considerations for demonstrating comparability to support pooling of all the clinical data are not well defined.
- Of concern are the multiple presentations of drug product and manufacturing sites. Specifically, there could potentially be fresh or frozen, 8 or 12 days, all at 2 different manufacturing locations. These details will complicate the CMC as well as the clinical data.
- Significant unmet need exists with currently existing CAR-T therapies do not work for many patients.
- The tri-specific nature of the therapy offers the potential to enhance efficacy based on more complete targeting; it's very exciting science.
- Strong ambition in the manufacturing time.
- The biggest weakness in my view is considering the clinical/commercial execution. How will non-specialty centers have the resources they need to prepare for appropriate care? How will they learn about what that looks like? A reasonably significant outreach effort is likely required, and that will need appropriate planning.
- Additionally, outcomes-based agreements are much stronger in principle than in practice; they are difficult to adjudicate and further research is required on this strategy.
- Additionally, from a patient access perspective, there is good thinking, but it's narrow in scope. This effort requires broader aperture and likely some external validation and pressure testing.
- This approach is attractive in that it could enable CAR-T therapies to be available at more centers, not only tertiary centers.
- The proposal presents practical mitigation strategies and an experienced infrastructure that substantially reduce execution risk.
- A novel trispecific CAR-T simultaneously targeting three B cell antigens addresses one of the major mechanisms of CAR-T failure (antigen escape) while incorporating a differentiated bicistronic architecture and dual costimulatory signaling.
- Claims that institutional cost can decrease to approximately $70,000 per treatment are attractive but remain projections rather than demonstrated real-world economics.
- While decentralized manufacturing is innovative, regulatory complexity, reproducibility across multiple sites, and quality oversight remain significant commercialization risks.
- Since there is only one manufacturing site, it would be helpful within the application to indicate how many lots need to be released each week or month in order to meet enrollment and treatment targets of the study and to indicate the experience of the facility to produce one product consistently at the indicated scale.
- It is unclear what outcome analysis will take place on the fresh vs frozen product. It seems positive results regarding a fresh product are needed to justify the new model of manufacturing closer to patients.
- The application proposes a thoughtful approach for trispecific CAR T cells targeting CNS and B-Cell Lymphomas. Concerns include lack of scientific rigor on Phase I plans. What's the power analysis to justify an additional 10 patients per cohort after identifying an MTD? Why not just run a Simon two stage design to initiate Phase II efficacy with an expansion cohort?

Value Proposition

- This trial aims to overcome a major limitation of currently approved CAR T-cell therapies: relapse driven by cancer cells losing or downregulating the single antigen (CD19) that existing therapies target. By engineering T cells to simultaneously recognize three B-cell surface markers a tumor would need to lose all three targets at once to escape treatment, which is far less likely than losing just one.
- For patients with refractory disease and post-transplant relapse there is a clear unmet need, and this approach provides a treatment option for patients that have none.
- Meaningful and substantial improvement would be evidenced by broader tumor recognition, reduced tumor escape, enhanced CAR-T cell persistence for longer, more effective duration of the response to therapy.
- The therapy has a plausible mechanism of action, with the possibility of reducing the potential for cancer cell escape.
- The autologous nature eliminates transplant rejection phenomena.
- Novel approach for administration of fresh, autologous drug product for patients that have unmet medical needs; very likely to be accepted by patients and HCPs.
- Significant unmet need exists with currently existing CAR-T therapies that do not work for many patients. The tri-specific nature of the therapy offers the potential to enhance efficacy based on more complete targeting. Significant pressure will be put on both the manufacturing costs and the ability to educate non-academic centers about the manufacturing process. Many centers may not have time and resources to dedicate to learning the approach, and this could hinder uptake. A rock-solid plan to build center capabilities up to this will be required.
- This approach aims to prevent relapse by overcoming tumor escape mechanisms and eliminating cancer cells more effectively than current single-target therapies.
- The study design effectively integrates manufacturing, logistics, and clinical execution.
- If fresh product can be infused, there are potential efficacy benefits.
- The idea of a central hub and spoke model's lower cost is unique and a creative concept to keep costs down.
- The trispecific approach, as proposed, for this patient population with high rate of relapse and poor outcomes could provide a good alternative to what is currently available for these patients who need better survival rates.
- There is significant unmet need, and, if successful, the approach could transform outcomes for a refractory disease. The work builds on previous CIRM funding.

Rationale

- The applicant proposes targeting all three B cell surface antigens at once, reasoning that broader target coverage should reduce the chance of antigen-loss relapse across a range of B-cell malignancies, including those with central nervous system involvement.
- Scientific rationale is for using tri-specific CAR constructs; it has been examined and evaluated for several years. The novelty feature is that each engineered T cell expresses two distinct CAR constructs (one targeting two antigens and another targeting the third antigen) from an optimized combination of (two) co-stimulatory domains. These T cells can detect and eliminate malignancies expressing any combination of the three antigens. Each CAR binds to its antigen independently, with optimal functionality. The Proposal calls this a "division of signaling labor".
- The IV route of administration is standard practice and single dosing would be expected to be sufficient. There is a caveat that high tumor burden may require fractionated dosing.
- The product has been tested through in vitro and in vivo studies. Work has been undertaken under a CIRM preclinical award and with subsequent efforts using healthy donor PBMCs, human B-cell lymphoma lines, NSG/ NSG xenograft mice. There is no human clinical data to date. The preclinical data generated was sufficient to support clearance of an IND.
- The rationale is sound with the triCAR approach. Autologous cells eliminate the GvHD concerns of allogeneic therapies.
- This science is quite exciting! The rationale and the CAR-T targets make sense, though there is some question about whether there is data to support a trispecific being stronger than a bispecific.
- The strategy is supported by an FDA-cleared IND, a comprehensive preclinical package, and a clearly defined first-in-human Phase I study designed to establish safety, dose, and feasibility.
- There is a discrepancy between the application and FDA communication regarding manufacturing days. While the application reads "Final Product Formulation and Harvest (Day 8 or 12)" the FDA communication indicates "the processes described in IND [# redacted) over a period of about 10-14 days."
- It seems the base case in the TPP for the product should be frozen with the optimal case being fresh.

- The rationale for the proposal is strong. However, the underlying premise is not adequately vetted. The idea that trispecific CARs are superior for overcoming heterogeneity has not been proven in vivo in comparison to bispecific CARs. At some point one would theorize that more CAR targets would begin to elicit a plateauing effect and experimental modeling that discerns these effects would be greatly appreciated.

Project Plan and Design

- The submitted clinical protocol document itself appears to be an inconsistently assembled file, mixing pages from two different protocol versions (Version 3.0 and Version 4.0) posing a document-integrity concern.
- The project plan being proposed is primarily to undertake the Phase 1/2a study to determine clinical safety and Phase 2 dosing. Activity 1 to get the trial up and running through the manufacturing and clinical sites captures the necessary elements, but 3 months may not be sufficient time to onboard all the initial sites.
- Fresh cell drug product (DP) (either 8- or 12-days vein to vein) will be logistically challenging. Cryopreservation will be used as a mitigation. Limited data was supplied from the applicant site that evaluated fresh vs frozen product on NSG Mice with Raji and the quality impact of differences in cell culture duration, both of which were summarized in regulatory correspondence. Data was sufficient for FDA responses and IND clearance.
- This project plan works for a single site manufacturing and treatment center. One site's role in this study is unclear - it is not listed in the Manufacturing Plan as a manufacturing site, though it will be performing manufacturing and treating patients. Relatedly, the approach for onboarding and assessing one or more CCCE sites for comparability to manufacturing practices and outcomes at the applicant site is not well-defined.
- There is a cleared IND, and future plans to seek RMAT based on positive Phase 1 data are appropriate.
- The CMC project plan is aggressive but likely manageable for approximately 4 dozen patients in the first study. More concerns will arise regarding how to meet the needs of a broader population if the therapy is successful here. Continuing to acquire data on fresh vs frozen DP will be key to the future success of this product. Also, the Sponsor will probably need comparability data generated for between the DP lots made at the proposed manufacturing sites in order to evaluate the entire patient population of data.
- The clinical trial design could be more carefully considered, and it is unclear how the team would advance from the initial 9 patients (3x3 design) to the larger cohorts. For the larger cohorts, clarity around the power analysis and efficacy outcomes would be helpful.
- It is unclear how the trivalent CD targeting is beneficial over a therapy that only targets one or two antigens. It is recognized that this may impact the likelihood of antigen escape, but more clarity would be beneficial to help justify the need for (and benefit of) the trivalent approach.
- The proposal includes thoughtful operational risk mitigation through validated logistics, chain-of-custody procedures, contingency manufacturing plans, and standardized safety monitoring.
- Multiple disease indications (ALL, DLBCL, CNS lymphoma, CML blast crisis, post-CAR relapse) introduce biological heterogeneity that may complicate interpretation of the study data.
- No current rationale as to why they would wait until EOP1 to submit RMAT. More recently RMAT is being granted with minimal # of patients treated if the data is strong. Even an investigator-initiated trial data sets have been successful.
- The project will generate data to enable stage appropriate go/no-go decision making for further investment in the approach.

Project Team and Resources

- The commercialization timeline (BLA submission by Year 7, commercial launch by Year 8) is long relative to typical for-profit development plans.
- Experienced project team. No concerns and this team appear to have strong collaboration support from other research institutions and not for profit organizations.
- The team’s leadership, expertise and staffing are appropriate to successfully complete all aspects of the project.
- The team has appropriate technical expertise for this project. The PI has other project interests, several of which are also CIRM funded. None appear to have overlap. It's unclear the PI has sufficient bandwidth to lead this project.
- The PI may be stretched thin and not able to devote sufficient attention to this trial to ensure success.
- The applicant GMP facility is suitable for manufacturing and testing Phase 1 cell products. However, the ability to deploy the manufacturing process for fresh and frozen products consistently and in compliance with GMPs to dispersed trial sites is unclear.

- Use of experienced, qualified vendors are appropriate to assure quality and reduce manufacturing risk.
- The team is experienced in early phase clinical development and clinical products.
- This program appears to have a reputable team in place and strong support from collaborating institutions.
- There is a lack of clarity regarding both the use of two different manufacturing sites and apparently up to 4 different manufacturing processes (8 vs 12 days, and fresh vs frozen).
- Collaboration with multiple sites, including CIRM's Community Care Centers of Excellence (CCCE) network, is designed to support decentralized patient care; the project also outlines clear plans for quality oversight and commercialization, indicating a mature operational strategy capable of supporting future multicenter expansion.

Population Impact

- The trial does not restrict enrollment by age, gender, ethnicity or race and aims to roughly mirror the state's population distribution.
- The applicant appears to understand the target indication, disease burden, care and health outcomes.
- Overall, the patient access plan is appropriate for the phase of development, but there are some additional hurdles that this asset will face which are not accounted for here.
- The patient access strategy bypasses traditional pharmaceutical markups, lowering the institutional cost to roughly $70,000 per dose and removing travel/financial burdens on patients, directly expanding access for underserved demographics, such as underserved agricultural communities in the Central Valley. Excellent thought and care are devoted to the diverse population impacted by this disease and how to make the treatment attainable locally.
- The strategy reduces travel burden and geographic barriers for patients in rural and underserved communities, particularly within California's Central Valley, while providing a scalable framework that could broaden access to future cell therapies.
- Efficacy and outcomes could have a significant positive impact if the therapeutic mechanism and manufacturing prove successful.
- The applicant’s plan for participant outreach, engagement, enrollment and retention addresses key barriers to trial participation by all affected population groups, is well-matched to the proposed study population and is feasible in the proposed time frame.

Application #	CLIN2-20454
Title (as written by the applicant)	An Oral Therapy to Inhibit Cancer Stem Cells.
Therapeutic Candidate (as written by the applicant)	It is a drug, [redacted candidate name], for patients to take by oral at home.
Indication (as written by the applicant)	Metastatic colorectal cancers (CRC)
Unmet Medical Need (as written by the applicant)	Metastatic CRCs have a 5-year survival rates of 13% for colon cancer, and 18% for rectal cancer. In California, there are 14,000-16,000 new CRC cases per year. CRC is the second leading cause of death, with 5,000 to 6,000 deaths in California, and more than 50,000 deaths in the U.S. per year.
Major Proposed Activities (as written by the applicant)	• Completion of Phase 1 dose escalation • Completion of a Phase 2 dose expansion in MSS-CRC following Simon two stage design • Manufacturing Active Pharmaceutical Ingredient (API) and oral dosing drug supply • Pharmacokinetic and pharmacodynamic analysis to determine drug exposure • Confirm mechanism in inhibiting cancer stem cells and other explorative endpoints • Biomarker analysis
Statement of Benefit to California (as written by the applicant)	CRC is the second leading cause of death, causing 5,000 to 6,000 deaths per year in California. Early onset of CRC is usually not detected by the current colonoscopy screening regimen, thus representing high risk of metastasis at diagnosis. The currently available therapies are not effective for microsatellite stable subtype (MSS-CRC), which account for ~96% of CRCs. MSS-CRC has higher incidence and mortality in Black Americans. The proposed project addresses the high unmet needs in MSS-CRC.
Funds Requested	$12,000,000
GWG Recommendation	**(1-84): Not recommended for 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: 80

Up to 15 scientific 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.

Mean	79
Median	80
Standard Deviation	4
Highest	85
Lowest	70
Count	15
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	1
Tier 2 (1-84): Not recommended for funding	14

FINAL 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.

Key Strengths and Weaknesses

- A molecule that works on some solid tumors, modifying metastasis is a definite need in advanced cancer, especially colorectal.
- The 60% complete-response rate when combined with anti-PD1 in the CT26 colorectal cancers (CRC) model, plus durable immunologic memory on tumor rechallenge is a compelling proof-of-concept.
- SUMOylation appears to be a viable anti-cancer target given the data with another compound. This approach seems to have limited toxicity.
- The value proposition is in the oral route of delivery and applicability to both solid and hematologic malignancies to be used in combination with immunotherapies where response rates are low.
- Valid scientific rationale; solid science; interesting target; commercial potential. Project team, project plan, clinical trial strategy, and plans for clinical trial execution are poor and not realistic.
- IND clearance (June 2024) and an active, dosing Phase 1 trial with patients already being treated. However, only 2 patients have been treated at the time of the proposal. The choice of only one clinical site is a concern.
- Primary issues with the proposal are feasibility, which includes the potential to enroll sufficient subjects at a single site and limited clarity on what data would encourage or discourage further combination studies with pembrolizumab or expansion into additional patients at the MTD.
- An IV version of a previous molecule inhibiting the same target was advanced into the clinic by a large pharmaceutical company and, while shown to be safe, was discontinued. Assuming the oral version is more potent as described, it is unclear why a large pharmaceutical company would not be interested in funding this work.
- Weakness: The proposal leans on the previous molecule's 109-patient safety database as supporting evidence, but the previous molecule has a different chemical mechanism and a different route of administration (IV vs. oral), so this is suggestive, not directly transferable safety data.
- Sufficient data are not provided on the criticality of effect on cancer stem cells (CSCs) to support clinical efficacy (over IFN effect) or specificity for CSCs.
- The clinical operations FTEs (all TBD), resources, and plan are insufficient to ensure a timely execution of the proposed single-site clinical trial.
- Enrollment challenges are anticipated with resources also not set in stone.
- There were limited clinical responses in solid tumors with a related drug, and it is not clear whether this drug, which is a covalent allosteric inhibitor, will be more active.

Value Proposition

- The value proposition for the product in the proposal centers on addressing a large, underserved market with a differentiated, more accessible drug for an indication with unmet medical need.
- The proposed therapy is a first-in-class oral therapy argued to inhibit cancer metastasis by targeting and eradicating cancer stem cells, although there was no discussion of proposed mechanism in the IB.
- The value proposition is in the oral route of delivery and applicability to both solid and hematologic malignancies to be used in combination with immunotherapies where response rates are low.
- Therapies for advanced MSS-CRC would be useful as these are currently limited.
- Based on the level of disease that exists, there is clearly a need for a new treatment and payers will understand that.
- The product addresses a major unmet need in metastatic microsatellite-stable colorectal cancer, a setting in which immune checkpoint inhibitors generally have limited activity and later-line systemic therapies typically provide modest and non-durable benefit. The proposed value proposition is that an orally administered, highly selective inhibitor for a specific SUMOylation pathway member could simultaneously suppress cancer stem-cell maintenance, reduce metastatic potential, and convert an immunologically resistant tumor into one responsive to pembrolizumab.
- Based on the literature, the current product can potentially be used in combination therapy to eradicate cancer stem cells (CSCs) of most solid tumors and blood cancers. The value proposition is outstanding. Patient populations could ultimately include metastatic CRC, triple-negative breast cancers, lung cancer,

other solid tumors, and blood cancers. There are no good options for treating metastatic CRC today, which has a 13% 5-year survival rate. This is worrisome in that there is already a disproportionate impact on those with more limited health care access and also on the troubling increase in CRC in younger populations that are currently below any screening considerations.

- The mechanism of action appears to be along two distinct and important paths. Besides inhibiting cancer stem cells directly, SUMOylation inhibition in immune cells activates anti-tumor immunity. In preclinical models of two solid tumors, the drug potently blocked metastasis. In addition, in a mouse model, a combination of the current product with anti-PD1 induced complete responses in 60% of the mice and induced formation of immunological memory.
- As this drug is administered orally, both patient access and patient compliance can be substantially increased.
- The specific case of metastatic CRC causes over 5,000 deaths in California and 50,000 deaths in the U.S. per year. In populations of low socioeconomic status and minority populations, this leads to later-stage diagnosis and worse outcomes.
- Currently, there is no FDA approved therapy or emerging therapies targeting CSCs for solid tumors.
- In the preclinical model that metastasizes to the liver, inhibition of metastasis was observed. In the breast cancer model, significant blockage of metastasis to the lung was observed.
- In the publication of the first-in-human clinical trial of the related compound, it was specifically discussed that the current product is another SUMOylation inhibitor with promising therapeutic effects. Therefore, advancing the proposed program is critical for translating the extensive scientific findings into patient benefit.
- The value proposition is fair, as this is a condition where additional treatments are needed, and a low 5-year survival.
- The proposed transition from an ongoing Phase 1 study into a Phase 2 expansion minimizes development delays while potentially improving patient access, particularly for patients in rural or underserved communities.
- If the 60% complete-response rate and tumor-specific immune memory observed in the preclinical model translated even partially to patients, the therapy could materially improve response durability, progression-free survival, and overall survival while reducing infusion burden relative to intravenous agents such as the related compound.
- Potential impact for metastatic colorectal patients via an oral small molecule is highly attractive.
- Payers will appreciate the focus in metastasis where unmet need is highest. OS as the primary or main endpoint will be crucial for value perception by payers; that is a key aspect of the disease burden story the company is conveying. Five years of data at launch would be outstanding; they will need some other indicators if less than five years of data are available at launch. Safety data will help differentiate if positive, but payers typically do not over-index on safety information and let patients/doctors make the choice they need. Dosing: oral is a positive from a patient/clinician standpoint, but payers do not "pay for convenience." National Comprehensive Cancer Network (NCCN) guidelines will be incredibly important to get on for strong access in oncology indications in the US. If the applicant secures 2A or better, access will be strong.
- It is unclear how CSC eradication supports/is critical for the justification for the proposed combination therapy.
- Very minimal/no access work done to date. This reviewer suggests doing more in terms of pricing and forecasting. The applicant should take a look at analog/references for pricing, speak to a vendor about market share/uptake, especially with a competitor coming to market.
- Questionable; appears to be not well thought out for execution.

Rationale

- Solid rationale and preclinical data; prior CIRM funding; FDA approved IND.
- Colorectal cancer treatments — chemotherapy, EGFR/VEGF-targeted therapy, checkpoint inhibitor combinations — leave a resistant CSC reservoir behind, which the proposal argues explains why metastatic microsatellite-stable CRC (96% of CRC cases) still has such poor outcomes (5-year survival of 13–18%), despite decades of treatment advances. No FDA-approved or late-stage therapy currently targets CSCs directly in solid tumors, so eliminating this pathway with the product is believed to address the proposed driver of relapse and metastasis.
- The applicant has suggested that the proposed therapy has potentially higher specificity and longer half-life and may also be safer than existing alternatives to justify further clinical development.
- Current therapies kill rapidly dividing cancer cells but leave behind cancer stem cells, which initiate the formation of new tumors, resulting in relapse and metastasis.

- SUMOylation inhibition esulted in a ~90% reduction in CSCs and reduction of self-renewal frequency by 90%. There also appears to be independent lab confirmation of the inherent underlying process. There appears to be a high level of specificity to the proposed treatment which offers the prospect for mitigating side effects.
- There is a first-in-human clinical trial at [redacted site], led by the PI, with a drug formulation that was supported by a DISC-2 grant.
- The drug has a long half-life, and its covalent inhibitors are expected to have duration of action that is governed by the enzyme's half-life and are therefore independent of the drug's stability in the blood.
- The efficacy is better than that reported for comparable treatments in the same model. And in that case, no immunological memory formation was demonstrated, which further supports the proposed treatment.
- The literature suggests that SUMOylation inhibition in cytotoxic T cells directly enhances effector function of cytotoxic T cells and ameliorates T-cell exhaustion.
- While there is not a good model for metastatic CRC, the approach was tested in the a model that metastasizes to the liver and inhibition of metastasis was observed. In the breast cancer model, significant blockage of metastasis to the lung was observed.
- The proposal demonstrates a logical and operationally feasible development plan that integrates safety, pharmacology, and efficacy assessments.
- The biological rationale is coherent and supported by multiple mechanistic layers: the targeted SUMOylation pathway member appears important for colorectal cancer stem-cell maintenance; inhibition reduces ALDH-associated stemness, and systemic SUMOylation inhibition can induce type I and type II interferon-related immune activation. The proposed product adds a differentiated molecular mechanism, oral bioavailability, prolonged target engagement, and chemo-proteomic selectivity, while the active metabolite retains similar activity.
- These findings justify clinical investigation, and the human experience with comparable treatments provides useful target-level safety and pharmacodynamic precedent. Important limitations materially reduce confidence, however: the most direct stem-cell limiting-dilution data were generated with a related compound rather than the clinical candidate; the metastasis studies were conducted in non-colorectal tumor models; one of the models is a single murine transplantable model and may overpredict immunotherapy responsiveness; group sizes appear small; and no human antitumor activity from the ongoing Phase 1 trial are reported.
- Data regarding SUMOylation and its role in stem cell biology exists. The preliminary data for the current approach is limited, specifically CSC targeting within clinical specimens as well as combination studies with immune checkpoint inhibitors.

Project Plan and Design

- A standard preclinical program has been completed and is sufficient to support clinical development.
- The Phase 2 statistical design targets an ORR improvement from a null of 8.4% to an alternative of 21% — clinically meaningful, but a fairly modest absolute response rate.
- The protocol includes well-defined safety oversight, Bayesian dose escalation, integrated biomarker analyses, and comprehensive project management.
- The ongoing Phase 1 trial has only just initiated a first cohort. It is noted that the original IB was dated November 2022.
- The proposal is to complete the ongoing Phase I trial and a Phase 2 trial and support manufacture of drug for the next phase. The proposal for the next phase would seem premature at this time.
- The program plans to enroll all patients at a single site. This does not appear realistic.
- Clarity is needed on how the trial will be feasible. It appears that staffing may be inadequate for the proposed sample size. In addition, more details are needed to demonstrate that the patient population is readily available for the study.
- The manufacturing plan benefits from an existing capsule formulation and clinical supply, but the application provides limited visibility into commercial process readiness, active-metabolite control, long-term stability, scale-up comparability, and supply contingencies. Risk mitigation is a notable weakness: the formal contingency section appears incomplete or minimally developed, and the proposal does not adequately quantify enrollment, manufacturing, or timeline risks, contingency costs, or non-CIRM funding coverage. On balance, the activities are directionally appropriate, but the plan needs sharper statistical decision rules, more realistic risk planning, and clearer evidence that the full objective can be completed within the stated budget and timeline.
- Accelerated approval is not targeted until ~2031, with commercialization dependent on pembrolizumab combination economics (partially offset by anticipated biosimilar entry in 2028) — a lengthy timeline during which competitive or regulatory conditions could shift.

- Several team members TBN/TBD; Phase I trial currently open. No clinical CRO selected or planned for; single site makes enrollment limited and unrealistic in current plan.
- For access and affordability, more market research is needed. It is way too light in this reviewer's opinion; forecasting needs to be done at a minimum, basic market analysis is missing. The applicant probably needs to provide more resources and funding to access and affordability/commercialization to make this clearer and more developed.
- Sufficient justification was not provided to support proposed biomarker strategy for the proposed population.
- MYC overexpression is proposed only as a 'potential' patient-selection biomarker — it is not yet validated, which adds execution risk to eventual patient stratification and commercialization strategy.
- Project plan and design are not that well thought out.

Project Team and Resources

- The team appears to be strong with a good plan to arrive at the deliverables.
- The team seems very lean for the proposed clinical trial. The budget does not appear to be well conceived.
- The applicant has proposed a single trial site (to enroll 90 participants) "due to the existence of expertise of the investigators and patient population." It is unclear whether the current clinical operations staff is adequate. Importantly, proposed conduct at a single study site does not reflect an urgency to enroll the trial to expedite clinical development and ultimate patient access.
- Lots of TBD personnel; not enough personnel to accomplish the goals.
- Many staff are listed as TBD, and there is concern that the team would be able to be put in place in order to complete this proposal in a timely fashion.
- Limited resources and potential enrollment challenges.
- The study team is not complete at this time. The proposed team and effort seems to be inadequate to fully carry out the trial.
- The team has strong academic discovery and investigator-initiated trial credentials, but the proposal provides limited evidence of collectively advancing a novel small molecule through late-stage development or licensure; it also does not directly address the criterion concerning stem-cell or genetic-therapy development, because this project is fundamentally a small-molecule oncology program rather than a stem cell-based or genetic therapy. The institutional environment is strong, but execution would benefit from additional experienced industry-level clinical development and CMC leadership.
- Inadequate and incomplete. Multi-site plan needed for Phase 2 trial. This study cannot be completed at a single site in a realistic time frame.

Population Impact

- Oral dosing is framed as both cheaper to manufacture and more accessible for underserved patients who cannot easily reach infusion centers.
- The value proposition proposed to broader communities is in the convenience of an oral therapeutic and the potential lower cost of manufacturing a small molecule drug.
- This may be effective across populations as a small molecule.
- The applicant understands the landscape and has provided the data around the initial target with the full understanding that the patient scope could increase radically.
- From an operational perspective, oral administration may improve treatment accessibility and reduce patient burden, while the inclusion of patient-reported outcomes and the emphasis on equitable access for rural and underserved populations strengthen the potential impact. However, enrollment may remain challenging given the requirement for patients who have progressed following multiple prior standard therapies.
- Inclusion criteria do not appear to exclude major demographic groups without scientific justification, which is a strength, but the applicant should establish more ambitious and evidence-based representation targets and a funded barrier-reduction plan to ensure that participation reflects the populations most affected by metastatic CRC.
- Strong potential impact. This reviewer would suggest specifically targeting a larger percentage of African-American patients given the prevalence and impact within this population.
- It is unclear why the proposed trial participant goal (Hispanic/Latino) is half as much as that of the current California population.
- Has potential but only planned for single site execution that will take a long time.