PDEV AWARDS

12/11/25

$121,985,050 **GWG RECOMMENDED**

$117,591,750 **CIRM TEAM RECOMMENDED**

$160,000,000 **AMOUNT AVAILABLE**

$0 **BOARD APPROVED**

								Score Range		Number of GWG Votes			
APP #	TITLE	BUDGET REQ	GWG Recmd	CIRM Recmd	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	Previous CIRM Funding	Early+Late; Late Only
PDEV-19137	Development of an AAV Epigenetic Gene Therapy for Intractable Chronic Pain Disorders	**$9,486,864**	**Y**	**Y**	**92**	92	2	88	93	15	0	Y	Early+Late
PDEV-19164	A First-in-Class CRISPR-CasX Gene Editing Therapy for Lowering Lp(a) to Prevent Cardiovascular Events	**$12,714,480**	**Y**	**Y**	**91**	91	3	85	95	12	0	N	Early+Late
PDEV-19141	[redacted] and Semaglutide to Treat Cardiometabolic HFpEF	**$10,571,220**	**Y**	**Y**	**90**	89	3	85	95	13	0	Y	Early+Late
PDEV-19150	A first-in-class CRISPR-CasX gene editor silencing APOC3 transcription for the treatment of Severe Hypertriglyceridemia	**$13,000,000**	**Y**	**Y**	**90**	89	2	85	90	12	0	N	Early+Late
PDEV-19140	CRISPR/Cas9-mediated gene editing of Hematopoietic stem and progenitor cells for Friedreich's ataxia	**$7,423,504**	**Y**	**Y**	**88**	87	4	75	95	12	2	Y	Late only
PDEV-19154	Late-stage development of [redacted], an UNC13A Targeting Antisense Oligonucleotide treatment for Amyotrophic Lateral Sclerosis, for IND-enabling studies	**$7,500,000**	**Y**	**Y**	**87**	86	2	82	87	10	2	Y	Late only
PDEV-19133	Stem Cell-Based Cartilage Tissue Regeneration	**$12,715,000**	**Y**	**Y**	**85**	86	2	85	90	14	0	Y	Early+Late
PDEV-19138	Noncoding RNA drug for arrhythmogenic cardiomyopathy	**$10,419,929**	**Y**	**Y**	**85**	86	2	85	90	14	0	N	Early+Late
PDEV-19156	Gene Therapy for Alpha-1 Anti-Trypsin Deficiency	**$5,916,702**	**Y**	**Y**	**85**	85	1	85	87	12	0	N	Late only
PDEV-19152	Advancement of a myotropic, liver-detargeting therapy for LGMD2i/R9	**$7,350,596**	**Y**	**Y**	**85**	85	2	80	87	10	3	N	Late only
PDEV-19149	Microglia replacement therapy for CSF1R-related Leukoencephalopathy	**$12,993,456**	**Y**	**Y**	**85**	84	4	75	90	6	6	Y	Early+Late
PDEV-19131	Autologous iPSC-derived progenitor smooth muscle cells for treatment of urinary incontinence	**$7,499,999**	**Y**	**Y**	**85**	83	2	80	85	8	6	Y	Late only

APP #	TITLE	BUDGET REQ	GWG Recmd	CIRM Recmd	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	Previous CIRM Funding	Early+Late; Late Only
PDEV-19139	Develop a human iPSC-based cell therapy for Canavan disease	**$4,393,300**	**Y**	**N**	**85**	81	8	60	90	9	5	Y	Late only
PDEV-19168	Epigenetic Gene Therapy for CDKL5 Deficiency Disorder	**$12,969,829**	**N**	**N**	**82**	82	3	75	85	3	10	Y	Early+Late
PDEV-19136	IND-enabling activities for a gene editing therapy for Duchenne muscular dystrophy	**$7,500,000**	**N**	**N**	**81**	80	4	70	84	0	12	Y	Late only
PDEV-19132	Preclinical Development of Targeted siRNA Nanoparticle Therapy for Autosomal Dominant Polycystic Kidney Disease	**$10,704,857**	**N**	**N**	**80**	80	4	70	85	2	11	N	Early+Late
PDEV-19165	Novel muscle-tropic AAV and RNA targeting strategy for safe and efficacious gene therapy for Duchenne Muscular Dystrophy	**$12,710,543**	**N**	**N**	**80**	79	6	70	90	1	12	N	Early+Late
PDEV-19135	A Novel Vasculogenic Stem Cell Product for the Treatment of Critical Limb Threatening Ischemia	**$7,499,998**	**N**	**N**	**80**	78	6	60	85	1	13	N	Early+Late
PDEV-19142	Universal hiPSC Skeletal Muscle Cell Therapy for Localized Atrophic Muscles after Chemoradiation in Sarcomas	**$12,998,288**	**N**	**N**	**78**	76	5	70	83	0	13	Y	Early+Late
PDEV-19161	A Novel Non-viral DNA Gene Therapy for Hypophosphatasia	**$12,670,039**	**N**	**N**	**75**	73	7	60	85	2	11	N	Early+Late
PDEV-19148	Autologous MPO Knock-Out Hematopoietic Stem/Progenitor Cells for Pulmonary Arterial Hypertension in Systemic Sclerosis	**$7,500,000**	**N**	**N**	**70**	71	5	65	84	0	14	Y	Late only
PDEV-19201	Gene therapy to repair muscle function in GNE myopathy (GNEM)	**$4,791,375**	**N**	**N**	**70**	70	3	65	75	0	13	N	Late only
PDEV-19172	Anti-miR-128 ASO, an antisense oligonucleotide therapy for heart failure and cardiac regeneration	**$7,366,847**	**N**	**N**	**70**	68	6	60	80	0	14	N	Early+Late
PDEV-19146	A Novel Non-viral DNA Gene Therapy for Calcium Pyrophosphate Deposition (CPPD) Disease	**$12,909,553**	**N**	**N**	**65**	69	8	60	85	1	13	N	Early+Late
PDEV-19129	IND-enabling studies for a 2nd Generation Vaccine Targeting Glioblastoma	**$5,029,306**	**N**	**N**	**65**	67	8	50	80	0	13	Y	Late only

Application #	PDEV-19137
Title (as written by the applicant)	Development of an AAV Epigenetic Gene Therapy for Intractable Chronic Pain Disorders
Therapeutic Candidate (as written by the applicant)	An epigenetic gene therapy that represses Nav1.7 for long-lasting chronic pain relief
Indication (as written by the applicant)	Trigeminal Neuralgia
Unmet Medical Need (as written by the applicant)	Trigeminal Neuralgia causes debilitating facial pain and has limited treatment options, often requiring invasive procedures. Our gene therapy offers a non-opioid, long-lasting approach that targets the molecular root cause to provide long-lasting pain relief.
Major Proposed Activities (as written by the applicant)	• Manufacture the gene therapy product to support first clinical trial • Safety Studies in Larger Animals • IND submission
Statement of Benefit to California (as written by the applicant)	An estimated 50 million Americans suffer from chronic pain, and in California, 45% of drug overdose deaths in 2018 involved opioids. We urgently need non-addictive alternatives. While our first indication is a rare condition, our gene therapy targets a key pain gene (SCN9A) involved in many intractable pain syndromes. If successful, this approach could reduce opioid dependence, improve quality of life, and offer lasting relief for Californians suffering from chronic pain.
Funds Requested	$9,486,864
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: 92

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	92
Median	92
Standard Deviation	2
Highest	93
Lowest	88
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	15
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel’s discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

Key Strengths and Weaknesses

- There is a critical unmet need for safe, effective, and durable treatments that address the underlying cause of Trigeminal Neuralgia (TN). Chronic pain associated with TN merits the label "suicide disease" because of the degree of suicides associated with lack of pain management. The proposed therapy is a gene therapy designed to durably silence NaV1.7, a voltage-gated sodium channel essential to pain signaling, through epigenetic repression of the SCN9A gene. It uses a repressor delivered by AAV9 directly to the trigeminal ganglion.

- This proposal presents a highly innovative program targeting NaV1.7 using a epigenetic gene-therapy approach. The scientific rationale is strong, supported by convincing human genetic validation and robust preclinical efficacy across human iPSC models and rodent pain models. The CMC and safety packages are appropriately planned but still maturing; potency assay qualification and long-term GLP toxicology remain critical path items. Despite these risks, the team's prior CIRM experience, mechanistic clarity, and clear clinical translation plan provide confidence in feasibility. Overall scientific merit is high, and the application meets the threshold for funding consideration, contingent on continued CMC and regulatory progress.

- Important clinical problem with high unmet need. Targets a molecule on nociceptors. May have role in other pain disorders.

- Large unmet need addressed with a new modality.

- Excellent proposal.

- The nonclinical testing strategy led to detailed description of ten nonclinical studies that have led to this application. In a series of six different studies in mice (4 different mouse models of inflammation; chemotherapy-induced pain; arthritis-induced pain and treatment-induced mechanical sensitivity) the applicants iron out effective dose, effective promoter, route of administration (subcutaneous vs intraperitoneal (IP)) and ability to effectively treat pain and demonstrate in situ repression of the target gene.

- The program carefully considers a definitive plan to IND. The team is well-positioned to meet the objectives. The intended clinical study population is appropriate and well-considered with the potential to develop a first-in-class therapeutic with significant potential and human need.

- Value Proposition:

    - Addresses a debilitating chronic disorder (trigeminal neuralgia), with currently suboptimal options fraught with undesirable side effects; thus there is clearly unmet need for novel effective long-term interventions.

    - The therapeutic candidate has key critical advantages over current therapies, notably precise targeting and selectivity for the pain-specific sodium channel through epigenetic repression of SCN9A gene transcription and use of specific promoters to limit expression to pain sensory neurons, which would mitigate off-target side effects of non-selective drugs.

    - The surgical route of administration is relatively non-invasive into trigeminal ganglion, as is routinely used for other TN treatments and can be done as an outpatient procedure.

    - The total AAV dose via this direct route is much lower than other clinical AAV therapies translating to lower cost of goods, lower toxicity, and comparable or reduced overall procedure costs.

    - The treatment has the potential for only a single procedure to durably alleviate TN and provide years of relief.

    - Only minor weaknesses are noted: Since TN is considered rare, there may be limited utilization of the therapy. However, if successful, there is future potential for expansion to multiple additional chronic pain conditions. Timing of the therapy may also be challenging since early intervention will likely have better outcomes but infeasible due to delays in patient identification and prolonged prior

pharmacologic trial and error.

- Rationale:
    - The selection of targeting Nav1.7 is based on a wealth of preclinical studies and clinical loss- and gain-of-function observations.
    - The selection of binding to target Nav1.7 transcription fused with a transcription repressor to durably silence Nav1.7 without introducing permanent genome changes (in contrast with more prevalent gene editing approaches) is novel and exciting.
    - The selection of the final lead product resulted from AI modeling and iterative engineering to achieve robust SCN94 downregulation (up to 97%) with no off-target changes.
    - Strong and convincing preclinical studies showed that targeted Nav1.7 down-regulation reduces pain symptomology across numerous chronic pain models including TN without evidence of side effects, and is durable for up to a year studied thus far.
    - Only minor weaknesses are noted: Most of the preclinical studies done thus far utilized intrathecal administration rather than intra-trigeminal as envisioned for the therapy. This will be resolved with the proposed additional studies. The TN study, which does use trigeminal ganglion injection, appears to be administered on the same day as the injury, but this is not a likely clinical scenario.
- Project Plan and Design:
    - Planned animal studies are well-designed to fill key gaps in the existing/prior data, in particular using direct unilateral TG injection as this is the envisioned therapy. Dose-ranging, minimum effective dose, biodistribution, toxicology/pathology, etc will be progressively determined from mouse TN models through rat and large animal subjects.
    - There is a planned compelling use of potentially important ddPCR (digital droplet PCR), which can detect rare occurrences /low levels of the product.
    - The CMC activities are a key strength of the project plan. Critical activities for ultimate generation of a GMP-grade product include master cell bank (MCB), high quality plasmid production, and generation of a GMP-compliant batch suitable for IND-enabling studies and clinical trials in sufficient quantity through early-phase clinical use.
    - The critical aspects of the CMC work will be done by CRO and work with Charles River Laboratories (CRL) is in place and is already initiated. CRL has extensive experience from start to finish of this process for high quality GMP-compliant bulk AAV production.
    - The applicant has been selected by CRL as part of their Cell and Gene Accelerator Program (CAP) for startups, and thus expedited and highly discounted clinical grade product is anticipated.
    - Interact meetings with FDA have provided guidance to proceed to the pre-IND stage. A regulatory plan is described and should be achievable within the proposed timeline.
    - Potentially expediting this process is qualification for Orphan Drug Designation. Work on this is planned with CRO Rare Moon, who focus on orphan drugs.
    - There are also details for planned future Phase 1/2a clinical trial, including double-blind placebo controlled design and dose escalation. A strength in the planned outcomes is use of comprehensive pain and quality of life assessments.
    - Only minor weaknesses are noted: There is some concern that AAVs such as AAV9 can produce DRG and TG neuronal toxicity. While thus far this has not been significantly observed with intrathecal injections, it is possible that toxicity could be exacerbated with the local intra-TG injections. In non-clinical studies, inclusion of some longer-delayed treatment groups and

older/aging groups could be important to more closely model the likely clinical parameters.

- Project Team and Resources:
    - The project team is led by a strong and ambitious PI.
    - The PI has assembled a talented team of experts, with particularly strong expertise in product/business development and regulatory affairs. A key component and strength of the plan is the inclusion of stellar CROs.
    - The team is supported by a strong scientific and advisory board, including collaborating leaders in the preclinical and clinical pain fields.
- Population Impact:
    - If successful, the ability to durably reduce debilitating TN using a single minimally invasive procedure could be game-changing for this clinical population.
    - The applicants have considered population and demographic factors that may impact participation and adoption.
    - Outreach and interactions with clinicians diagnosing and treating TN and Face Pain Association are planned for increasing awareness and recruitment.
    - Communications will also be translated to Spanish and culturally tailored to reach the large California Hispanic/Latino population, who may be underdiagnosed and undertreated for TN.

Value Proposition

- Trigeminal neuralgia (TN) is a chronic facial pain disorder that can be debilitating, with intense episodes of painful paroxysms, occurring up to 50 times/day, resulting from normal stimuli such as chewing, speaking, smiling, touching the face, etc, additionally leading to withdrawal from social and work activities and possible suicidal behavior. It could affect thousands of individuals in California and beyond. The primary cause is thought to be due to compression of the trigeminal nerve by aberrant blood vessels. Women are affected twice as often as men, and diagnosis increases with age.
- Currently available medications (e.g. Na-channel blockers such as carbamazepine) are first line treatments, which provide good initial pain relief but have significant side effects and reduced effectiveness over time, diminishing their long-term utility. Surgical options such as microvascular decompression can work but may risk nerve damage leading to facial numbness, hearing impairment and other issues, are major surgery, are expensive, and may need to be repeated due to high recurrence rate. Thus there is a clear need for novel effective therapies for TN management.
- Key and critical advantages of the new therapy are: 1) Precise targeting and selectivity for Nav1.7 repressing transcription and specific promoters to limit expression to pain sensory neurons, which would preclude off-target side effects of non-selective drugs, local administration to avoid systemic side effects (as well as reduce AAV/gene toxicity or antibody development) and 2) the potential for only a single procedure to durably alleviate TN and provide years of relief.
- The surgical route of administration is also relatively non-invasive (into trigeminal ganglion (TG) - Meckel's cave, as is currently routinely used for other TN treatments, under fluoroscopic or CT guidance. It can be done as an outpatient procedure.
- Trigeminal neuralgia is an excruciating chronic pain disorder that has a significant negative impact on patients' lives.
- Some patients commit suicide because of the severity of the pain.
- Standard treatments are not effective in most cases - so the expected impact on an unmet medical need is

substantial.

- The product offers advantages over current therapies by providing durable, potentially multi-year pain relief from a single injection, compared to daily medications (40% discontinuation rate due to side effects) and surgical interventions requiring repeated procedures (30-78% recurrence rates depending on procedure type). The therapy targets NaV1.7 selectively in sensory neurons, avoiding the systemic side effects of non-specific sodium channel blockers like carbamazepine.

- The therapy tackles a critical gap for trigeminal neuralgia patients, often called the "suicide disease," where current treatments provide only temporary relief with significant burdens. With 50% of patients ultimately requiring surgery and many undergoing multiple failed treatments, the mechanism addresses the underlying pathophysiology rather than just suppressing symptoms.

- The total AAV dose via this direct route is much lower (est. 1000-fold) than other clinical AAV therapies translating to lower cost of goods, and overall procedures would be comparable to or lower than current surgical TN treatments. Lower AAV dosage would also likely reduce toxicity.

- The proposed product demonstrates superior economics with cost of goods under $1,000 (enabling pricing comparable to existing surgical interventions at $30,000-$40,000) due to 1,000-fold lower AAV dosing versus systemic gene therapies. The delivery uses an established outpatient procedure already employed for glycerol rhizotomy, requiring no new surgical infrastructure and eliminating the need for repeated surgeries ($3,000 per glycerol injection every ~3 months) or chronic medication costs.

- Preclinical efficacy across six pain models (neuropathic, inflammatory, arthritic, and visceral pain) positions the product for expansion beyond trigeminal neuralgia to other intractable chronic pain conditions such as osteoarthritis, diabetic polyneuropathy, and low back pain through condition-specific delivery routes, addressing a massive unmet need where NaV1.7 has proven refractory to small molecule inhibition.

- TN is considered rare and, of the potential TN candidates, possibly less than 25% may utilize the therapy, due to predominant pharmacotherapies and other surgical options giving some relief to the majority of TN patients. However, if successful, there is future potential for expansion to multiple additional chronic pain conditions.

- Timing of the therapy may also be problematic since early intervention will likely have better outcomes but infeasible due to delays in patient identification and prolonged prior pharmacologic trial and error.

- Women are affected twice as often as men, and diagnosis increases with age. While both sexes will be studied in preclinical models, evaluations in older animals are not addressed.

Rationale

- The therapeutic candidate is a gene therapy designed to durably silence Nav1.7, a voltage-gated sodium channel essential to pain signaling, through epigenetic repression of the SCN9A gene (α-subunit of the Nav1.7 channel). Nav1.7 is primarily present in nociceptors (in dorsal root ganglia and trigeminal ganglia) and has been well studied a playing a key role in pain signal transmission, driving dorsal root ganglion (DRG) nociceptor hyperexcitability, and upregulation in chronic pain states.

- To provide precise and durable SCN9A transcription suppression without introducing permanent genome changes, a programmable DNA-binding domain targeting Nav1.7 DNA binding fused with a transcription repressor will be used. Thus long-term transcriptional silencing of Nav1.7 can be achieved without editing the genetic sequence (unlike gene editing approaches). It will be delivered by AAV9 directly to the trigeminal ganglion (TG).

- An AI-driven platform developed by a cofounder enabled rapid and potent design of editors to select the most promising candidates. Rationale for superiority of this approach vs others is well-described.

- The work has been in development by the PI and team for the past 10 years, partially supported by prior CIRM funding (DISC2) and recently funded TRAN1 (through pre-IND, will be withdrawn if this PDEV is funded). Both early and late PDEV phases are included, with the goal of completing the IND-enabling

package and prepare for clinical trial initiation (Phase 1/2a).

- For clinical translation, lead candidate was selected using human iPSC-derived nociceptors, gain-of-function disease relevant patient derived iPSC nociceptors, and human TGs, showing robust SCN94 downregulation with no off-target changes, and electrophysiological confirmation.
- Strong and convincing preclinical studies by this group showed that targeted Nav1.7 down-regulation (e.g. using a surrogate that targets the mouse Scn9a) reduces pain symptomology across numerous chronic pain models, including TN, without evidence of side effects. Impressive published results indicate durable analgesia (~ 1yr) in an inflammatory pain model following a single intrathecal injection, and no numbness in controls.
- Most of these use the intrathecal administration approach, but there are new data showing effectiveness in a mouse trigeminal neuralgia model, showing decreased mechanical allodynia, cold sensitivity, and marble burying (depression).
- The target rationale is anchored in loss-of-function mutations in SCN9A (encoding NaV1.7) cause congenital insensitivity to pain with no other neurodevelopmental alterations. This provides validation for NaV1.7 in human nociception, establishing a scientific foundation for therapeutic intervention. The approach directly addresses why small molecule inhibitors have failed (lack of selectivity among NaV subtypes causing cardiac/CNS side effects) by using gene-level repression with high specificity.
- The therapy demonstrates disease-modifying activity in six distinct rodent pain models, including inflammatory, neuropathic, arthritic, and the disease-specific trigeminal neuralgia model. Efficacy is consistent with statistical significance, and durability extends to 308 days in the inflammatory model suggesting the approach addresses chronic pain, not just acute symptoms.
- Compelling nonclinical package.
- Preliminary studies, funded by CIRM, demonstrate efficacy of this one-time, locally delivered gene therapy that is designed to durably repress expression of NAv1.7 voltage-gated sodium channel.
- The therapy is a locally administered treatment into the trigeminal nerve.
- While the breadth of models is impressive, some limitations exist. The TN model uses only small cohorts though effect sizes appear large. iPSC-derived nociceptors, while disease-relevant, may not fully recapitulate in vivo TN pathophysiology including immune and glial contributions. The published durability data uses intrathecal delivery rather than the proposed direct trigeminal injection route, and large animal safety data is limited to 8 days. GLP toxicology studies with the final clinical route are planned but not yet completed.
- A potential limitation in some of the preclinical pain models, e.g. the mouse TN model treatment timing which appears to be administered on the same day as the injury (although the figure (fig. 7) is not well-described). It seems important to determine whether reversal of TN can be achieved with a delayed treatment.
- Minor: There is some confusion with regard to the final lead product, in some case listing one promoter as lead candidate, with a proprietary Nav1.7-specific promoter as backup (e.g. table p. 50) and opposite in some cases (e.g. table p. 51). The introduction of the former promoter in the narrative is abrupt (Fig. 9 mouse intrathecal safety studies and subsequent Fig. 10 intrathecal safety/tox studies) and is not initially explained.
- There is minor concern that Nav1.7 may be insufficient for targeting clinical TN, since a small molecule blocking Nav1.7 (vixotrigine) for TN clinical trials has been discontinued.

Project Plan and Design

- Proposed experiments follow a logical progression toward the approval of an IND.
- Experiments in large animals will evaluate both males and females (an important consideration because

trigeminal neuralgia occurs in women more frequently than men).

- Planned animal studies are designed to fill key gaps in the existing/prior data, in particular using direct unilateral TG injection as this is the envisioned therapy (most preclinical work has been intrathecal route). In addition, dose-ranging will done progressively: mouse TN behavioral testing in order to establish the minimum effective dose, followed by rat biodistribution and neuronal transduction. Pilot studies in large animals with necropsy at day 28 will be done for clinical monitoring, neurological function, toxicokinetics, vector shedding, biodistribution, histopathology, etc. Together, these are intended to optimize vg/dose.

- There is use of potentially important ddPCR (digital droplet PCR), which detect rare occurrences/low levels of the product confirming expression at local injection sites, but also perhaps undesired extra-TG tissues or fluids. (using ddPCR assays that will be developed as part of the CMC activities).

- The planned studies are overall well designed, with appropriate n's and inclusion of both males and females. Following pre-IND feedback, a 6 month GLP toxicology, biodistribution, and immunogenicity study with several doses is planned in the large animals.

- There are still timing details with regard to AAV administration in the mouse model missing.

- Mitigation in the event of TG or other pathology in the follow-up rat and large animal evaluations, particularly in higher dose ranges if guided by mouse TN pain reduction dose ranging, is not addressed.

- It may also be helpful to include some longer-delayed treatment groups and older/aging groups to more closely model the likely clinical parameters as described in the background.

- The CMC activities are a key strength of the project plan. Critical activities for ultimate generation of a GMP-grade product include master cell bank (MCB) for manufacturing, high quality plasmid production, characterization, stability testing, etc., and generation of a GMP-compliant batch suitable for IND-enabling studies and clinical trials in sufficient quantity through early-phase clinical use. Fill and finish plans into final vials for clinical use and long-term storage are also described. Separately, a biologically relevant potency assay to measure repression of Nav1.7 is being developed.

- The critical aspects of the CMC work will be done by CRO. For this purpose, work with Charles River Laboratories (CRL) is in place and is already initiated. The applicant organization has been selected by Charles River Labs as part of their Cell and Gene Accelerator Program (CAP) for startups, and thus expedited and highly discounted clinical grade product is anticipated. CRL has extensive experience from start to finish of this process for high quality GMP-compliant bulk AAV production (over 20 GMP-compliant kits produced each year, with most being AAV vectors). A detailed manufacturing and scalability process and timeline is presented, including contingencies for unexpected delays or batch failures, and appears feasible. Since the average lot size for AAV9 products is much higher than that needed for small targeted TG injections, it is estimated that the batch would produce 10K – 100K doses, well over the amount needed.

- Clinical: Clinical leadership and advisory personnel, clinical protocol development, recruitment feasibility, statistical modeling, etc. are briefly described. Preparation for regulatory submission (Investigator Brochure summarizing CMC, nonclinical, and clinical design) and IRB/biosafety packets are also mentioned. While initiated during year 2, these aspects of the project are presented in less detail as the bulk of the work will be done as late PDEV and guided by early PDEV work. Some of this work will also be done using CROs.

- Regulatory activities are also described. Interact meetings with FDA have already been requested and guidance provided to proceed to the pre-IND stage. Brief meetings with the European Medicines Agency was also held that provided additional feedback and constructive suggestions. A regulatory plan moving forward is described and should be achievable within the proposed timeline, with pre-IND meeting planned for early part of year 2, and IND meeting held in year 4.

- Potentially expediting this process is qualification for Orphan Drug Designation, for which there is already a precedent in other TN trials. Work on this is planned with CRO Rare Moon, who focus on orphan drugs. Commercialization pathways are also envisioned.

- There are also details for planned future Phase 1/2a clinical trial, including double-blind placebo controlled design and dose escalation, with inclusion and exclusion criteria and enrollment targets. Consent, evaluation

scheduling, DSM, etc are included in some detail. The number of planned follow-up visits and in-clinic evaluations may become unwieldy and lead to some under-compliance to strict adherence.

- A strength in the planned outcomes, although primarily to evaluate safety and tolerability of single trigeminal injection of the product in TN patients, is use of comprehensive daily electronic pain diaries to assess pain frequency and intensity particularly for TN paroxysmal attacks, and use of a breadth of validated instruments to assess changes in quality of life and functional status, including sleep interference, physical and social activities, anxiety/depression, pain catastrophizing.

- There is some concern that AAVs such as AAV9 can produce DRG and TG neuronal toxicity (and possibly showing early indications of this trend in initial mouse pathology tests; fig. 9). While noted as a potential risk, and addressed as part of the planned GLP-Toxicity studies, and thus far not been significantly observed with intrathecal injections, this toxicity could be exacerbated with the local intra-TG injections, and management of this should it arise has not been addressed.

- The 4-year timeline to IND clearance is ambitious but achievable given existing proof-of-concept data and lead candidate selection already complete. Strengths include: established CRO relationships, experienced team with prior IND submissions, and concurrent CMC/regulatory/clinical planning activities. However, potential bottlenecks exist: 6-month GLP-tox study (Q3 Year 2-Q2 Year 4) consumes half of Late PDEV timeline leaving limited buffer for study amendments or FDA feedback incorporation; large animal availability marked as "medium likelihood/high impact" risk; and potency assay development identified as "medium likelihood/high impact" risk requiring parallel development of two assay systems. The proposal acknowledges these risks with mitigation strategies but timeline success depends on seamless execution across multiple critical path items.

- The risk matrix systematically addresses likely failure modes across CMC, regulatory, nonclinical, and clinical areas with specific mitigation strategies and quantified contingency costs. Key strengths include: (1) Manufacturing—backup CDMO identified (PackGene), biweekly joint reviews with Charles River, contingency funds for slot rebooking or repeat runs; (2) Potency assay—parallel development of two assay platforms with backup CROs identified; (3) Large animal studies—multiple CRO options identified including backup sites with TG injection expertise, neurosurgeon consultant available for difficult injections; (4) Clinical enrollment—University of Minnesota site treats 1,300 TN patients annually, advocacy partnerships with Facial Pain Association, ability to broaden entry criteria. Notably, all contingency funds ($2.8-3.5M total) are covered by planned seed financing from Ysios Capital, demonstrating financial preparedness beyond CIRM funding.

- Mitigation strategies have been considered to reduce potential immune response to AAV9. However, there is no discussion of treatment or alternatives should seroconversion or untoward inflammatory responses occur.

Project Team and Resources

- Great team and board.

- Primary team consists of individuals in gene therapy R&D, translational medicine, and regulatory and business expertise.

- The team is supported by a very strong advisory board (i.e., known experts in basic and clinical pain research).

- The applicant organization will collaborate with the Facial Pain Association to support outreach and education.

- Plans are in place to support patients to participate in the proposed study (e.g., support for costs of transportation, housing, lost wages).

- Preliminary considerations were given to how to enhance enrollment, support retention, and provide culturally relevant information to potential participants.

- The team expertise and plan to advance to IND are fully captured in the proposed plan.
- The project team is led by a strong and ambitious PI. The PI conceived this program during their PhD studies, and co-founded the company with the President and CSO in 2019. The PI has also led a number of grants, which have resulted in a large package of supportive preclinical data in several species, chronic pain models, safety and toxicology studies, and in vitro product screening and development, which will all be important and included going forward towards IND-approved studies for TN and later additional chronic pain indications.
- The PI has assembled a talented team of experts, with particularly strong expertise in product/business development and regulatory affairs. The President and CSO will lead AAV manufacturing, CRO management, and regulatory interactions. The VP, Toxicology & Regulatory Affairs lead, has career-long experience from start-up to established companies in GLP toxicity and regulatory submissions. The Executive Chair has brought multiple gene therapy products to market, guiding cell and gene therapy projects from R&D through CMC to commercialization. The CMO is bringing clinical leadership in AAV-based gene therapies. The team is supported by a strong scientific and advisory board, including collaborating leaders in the preclinical pain field, clinical pain trials, AAV expertise, Nav1.7 biology, and gene therapy, with others being recruited.
- A key component and strength of the plan is the inclusion of stellar CROs, most notably Charles River Laboratories, who will perform the essential GLP large animal toxicology, AAV9 GMP manufacturing and process development in their extensive testing and manufacturing facilities.
- An extensive and strong packet of supportive collaborative letters is included.
- Together the investigators have prepared a well-written, comprehensive application with consideration of all aspects from product inception to completion.
- The proposal outlines systematic coordination including weekly internal meetings, quarterly joint SAB reviews, structured workstreams for nonclinical/manufacturing/regulatory/clinical planning, and biweekly joint review meetings with Charles River to prevent delays. A dedicated Program Manager will handle grant coordination, reporting, and milestone tracking. Cross-functional integration occurs through written reports and shared PI/CSO decision-making, with conflict resolution escalating to senior leadership and independent arbitration via Board of Advisors if needed.
- The staged approach with clear go/no-go decision points demonstrates thoughtful risk management. However, coordinating 4+ major CROs (Charles River, RareMoon, IQVIA, multiple assay development vendors) plus advisory board input across 4-year timeline with a small internal team represents significant complexity—success depends critically on the yet-to-be-hired Program Manager's capabilities and the PI/CSO's bandwidth to maintain oversight quality across parallel workstreams.

Population Impact

- Applicant provided detailed information on what is known about the epidemiology of trigeminal neuralgia and associated high risk groups.
- There are no current treatments that can effectively target the root cause of this rare TN disease and this would be a first-in-class therapy that could benefit thousands of Californians and beyond. The intended clinical study population is appropriate and well-considered.
- The primary value of this proposed therapy would be the ability to durably reduce debilitating TN using a single minimally invasive procedure. If successful, this could be game-changing for this clinical population. The applicants have considered population factors that may impact participation and adoption. Notably, as TN disproportionately affects older adults and females, it is anticipated that the target population will be similarly distributed.
- Somewhat puzzling is the seemingly low reporting or identification of Hispanic/Latino ethnicities with TN, either locally, U.S., or globally (1%), in contrast with other demographic groups, particularly White and Black, and confirmed by a collaborative study done with the applicants. This is particularly surprising considering California demographics with 40% Hispanic or Latino, and may suggest impediments to the recognition of

TN and/or availability of treatment options in this population. To potentially address this, outreach materials will be translated to Spanish and culturally tailored.

- Affordability of the treatment has also been considered, and a patient assistance program will be developed to minimize out-of-pocket costs for uninsured or underinsured patients. Initial orphan drug positioning will be leveraged.

- Since TN is a rare disease, patient recruitment and adoption can be challenging. This is acknowledged and contingency plans to enhance interest and recruitment are being initiated, including the interactions with the Face Pain Association, presentation at the Annual Face Pain Conference, and outreach with clinicians diagnosing and treating TN (letters of support are included).

- There may be some additional issues with regard to willingness to participate in early clinical trials, since only one dose will be administered (which may be sub-effective), with no repeat dosing, and some patients will receive placebo. In addition, an exclusion is patients not willing to give up their current TN analgesic medication, which may further discourage potential participants.

- Since better treatment outcomes for TN result from early intervention, which is often unavailable to patients of lower socioeconomic status, access and timing need to be considered for this new therapy.

Application #	PDEV-19164
Title (as written by the applicant)	A First-in-Class CRISPR-CasX Gene Editing Therapy for Lowering Lp(a) to Prevent Cardiovascular Events
Therapeutic Candidate (as written by the applicant)	[redacted candidate] is a novel CRISPR therapy that targets the LPA gene to permanently reduce Lp(a), a key genetic driver of cardiovascular disease (CVD).
Indication (as written by the applicant)	Prevention of atherosclerotic cardiovascular disease in adults with genetically elevated Lp(a)
Unmet Medical Need (as written by the applicant)	Lp(a) plays a causal role in CVD. Unlike LDL, it is unaffected by lifestyle or statins. Elevated Lp(a) increases the risk for coronary artery disease, stroke, peripheral artery disease, and aortic valve stenosis. Despite its impact, Lp(a) remains underdiagnosed, and there are no approved therapies.
Major Proposed Activities (as written by the applicant)	• Finalizing data package to evaluate potency, safety and efficacy of [redacted candidate] • Preparation and conduct of a pre-IND meeting with the FDA • Completion of IND-enabling studies and preparation for IND submission
Statement of Benefit to California (as written by the applicant)	[redacted candidate] represents a groundbreaking California-developed genetic therapy aimed at eliminating Lp(a)-driven CVD risk. It targets a genetically determined risk factor for which there is no available treatment. By advancing this precision medicine approach, this program has the potential to reduce the burden for people living with high levels of Lp(a), the financial impact on healthcare system, and establish California as a leader in curative therapies that improve public health and save lives.
Funds Requested	$12,714,480
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: 91

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	91
Median	91
Standard Deviation	3
Highest	95
Lowest	85
Count	12
(85-100): Exceptional merit and warrants funding, if funds are available	12
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

What are the key strengths and weakness that influenced the final score?

- A possible once in a lifetime intervention meaning it has advantage over current competitors even if they are further on in clinical testing.
- Strong rationale for the approach and the clinical need - innovative technology; strong team; early but compelling.
- Though there are competitors and several companies now targeting Lp(a), the value proposition offered by a single treatment option for lifelong effect was considered a major advantage and a major potential advancement for the field.
- The scientific rationale appears sound. From a CMC perspective the manufacturing plan is well designed and follows a standard template for gene editing with liposomal delivery. It is still very early in the development and while the manufacturing plan is well defined there still is much work to do to identify vendors and develop the detailed process development, manufacturing, analysis and release testing plans.

Does the project hold the necessary significance and potential for impact?

- Lp(a) is a realistic target in secondary prevention of cardiovascular disease. It has a great deal of evidence to support this as a key target. Key advantages of the therapeutic candidate includes:
    - Single-administration durability: A one-time therapy that removes the burden of lifelong adherence at clinically relevant doses.
    - Improved potency: Engineered nuclease activity enables lower doses of LNP, lessening the primary toxicity associated with LNP based gene therapies.
    - KIV2 (Kringle IV type 2) independent targeting: Effective across genetically diverse populations, including those with different numbers of KIV-2 repeat alleles.
    - Mechanistic mimicry of natural protection: Frameshift editing recapitulates known genetic variants linked to reduced Lp(a) and cardiovascular risk.
    - Clean safety profile: No measurable off-target activity in primary human hepatocytes at supersaturation doses. This is a strong summary of the strengths.
    - Validated LNP delivery: Unclear of actual LNP tech and it is unclear why not using GalNaC (N-Acetylgalactosamine).
- There is substantive unmet clinical need and a massive population globally that "could benefit". Value proposition was not fully thought through, but if life long can be realistic. A lot of competition ahead of this in ph2/3 but the USP here is the life long benefit.
- A single treatment option for lifelong effect could have a significant impact.
- The applicants propose a gene editing approach to lower lipoprotein(a) and reduce the risk of atherosclerotic cardiovascular disease. The disease has a relatively high prevalence and there are two investigational siRNA agents, olpasiran and lepodisiran, that are in Phase III trials and show promise. Nevertheless, a one

time gene modification treatment would have a compelling value proposition.

Is the rationale sound?

- Editing by this mechanism (gRNA; CasX) seems very efficient and no measurable off target effects to date. The rationale is clear for a one-time treatment with the LNP homing to the liver exclusively via GalNAC and the efficiency of the gRNA design already shown and the CasX system delivery via mRNA. The key advantage is one-time improving compliance. There are in-field competitors here with ASO and siRNA and the trials are looking excellent - however they require repeat delivery (3-6 months) and compliance and adherence for this is not clear/predictable. The data so far is compelling *in vitro* and *in vivo* (2 mouse models) and some large animal model assessments. So far, efficacy is high and safety clear.
- Since Lp(a) levels are almost entirely dependent on genetics, this is an attractive target for permanent editing.
- The editing efficiency and the lack of detectable off-target editing with the prototype is impressive.
- The scientific rationale appears sound. From a CMC perspective the manufacturing plan is well designed and follows a standard template for gene editing with liposomal delivery.

Is the project well planned and designed?

- The project has a clear plan through activities stated that are entirely logical.
- The 3 stage development program is well thought out and organized.
- The regulatory interactions are appropriately planned which will ensure timely feedback regarding the use of large animal models and surrogate products for IND-enabling studies.
- It is still very early in the development and while the manufacturing plan is well defined there still is much work to do to: identify vendors and develop the detailed process development, manufacturing, analysis and release testing plans.

Is the project feasible?

- The team has consistently developed the approach with iterations and generations of molecules that have been developed. The gRNA sequence, the CasX generation - the LNP is in-licensed. A robust plan is clear and aligned to the experience of the team in the commercial environment. Environment and facilities look strong. This reviewer is unclear of company funding levels to predict the viability of the company over time.
- The team looks appropriately organized.
- The project team appears appropriate with adequate resources.

Does the project include considerations for maximizing the impact of successful outcomes across affected populations?

- Globally would have value and in the USA on a mass scale (1/5 have elevated Lp(a)). Also reaches into ethnicity where higher rates are seen in some instances. The health economics is well thought through at this juncture and there are clear advantages as a one time treatment. Risk is whether multiple doses are ultimately needed for the perceived efficacy in the first place. Clear milestones and success criteria in the TPP are evident.
- The applicants indicate that Lp(a) remains underdiagnosed and undertreated but it's not clear if there will be efforts to increase awareness or testing of potentially affected populations.

- Very little was described in the application.

Application #	PDEV-19141
Title (as written by the applicant)	[redacted] and Semaglutide to Treat Cardiometabolic HFpEF
Therapeutic Candidate (as written by the applicant)	The therapeutic candidate is a combination of a small RNA drug (anti-inflammatory) and a GLP-1 agonist (anti-obesity)
Indication (as written by the applicant)	The target indication is heart failure in obese patients.
Unmet Medical Need (as written by the applicant)	Heart failure with preserved ejection fraction (HFpEF) represents >50% of the 6 million heart failure patients in the US. HFpEF patients experience frequent hospitalizations and 5-year mortality is >50%. There are very few therapies and none that halt disease progression or improve survival.
Major Proposed Activities (as written by the applicant)	• Dose-ranging and efficacy studies for therapeutic optimization in preclinical heart failure models • Complete drug manufacturing and toxicology testing • Prepare and conduct a pre-IND meeting with FDA
Statement of Benefit to California (as written by the applicant)	The burden of heart failure with preserved ejection fraction (HFpEF) in California is significant and growing. HFpEF prevalence is estimated to be between 1.1% and 5.5% of the population. HFpEF is a significant public health concern due to its association with poor quality of life, increased hospitalizations, and early mortality. There are no drugs that halt HFpEF progression or reduce mortality. Effective HFpEF drugs will improve the quality of life for citizens of California.
Funds Requested	$10,571,220
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	89
Median	90
Standard Deviation	3
Highest	95
Lowest	85
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	13
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

Key Strengths and Weaknesses

- Well designed. Good large animal model planned. Straightforward CMC.
- Clear unmet need. Heart failure treatment landscape is changing but mortality remains high.
- Significant unmet need and value proposition to address root cause of disease.
- The value proposition of this application is high. The expert team has direct experience in developing drug candidates in the space and are building on fundamental learnings logically.
- Preliminary data in relevant animal models of disease for the proposed approach.
- Innovative compound and development. Strong clinical team and development plan. Cost of goods likely not prohibitive.

Value Proposition

- Heart failure is a major area of clinical need across California, the USA and globally. There are ethnicity and gender inequalities in addition to the general population need. HFpEF, being targeted here, is a substantial part of the heart failure (HF) community and current drug regimens are continuing to improve treatment, but effects on mortality are less clear. There are constant improvements in treatment of HFrEF and HFpEF as major trials come to their conclusions, but a clear need is there for novel therapeutics. The therapeutic here would be easily given as a combination. Uptake would therefore seem fine, a combination of the two (not a single polypill).
- Significant unmet need and value proposition for combination therapy.
- Very high value proposition. Prevalent indication with low unmet need and line of sight to low cost of goods.
- Large unmet need. Cost of goods will fall.

Rationale

- The drug has come from long standing work on cardiospheres and mining the cargo of the extracellular vesicles (EVs) from these spheres. The product is from the ncRNA Y genes in the EVs and has been bioinspired from the original sequence in the EVs. Robust evidence across models of an anti-inflammatory and anti fibrotic effect to support the HFpEF focus.
- Target mechanism of action has been nailed on with the ultimate effect of increasing the expression of a gene to alleviate stress responses. Works through immune modulation, such as improving IL-10. A body of evidence supports this. A prior CIRM grant has developed a compound as an oral therapeutic and this looks quite simple and effective. A pig model of HFpEF has been created for use in this study.
- There is preliminary data for both monotherapies and proposed combination therapy in relevant animal models of disease.
- There is an understanding of potential complementary mechanisms of action of the proposed combination

therapy.

- Potential to target root cause of disease supports value proposition of potential decrease in mortality.
- Builds on foundational data with the RNA alone; clear benefit of combination.

Project Plan and Design

- A logical series of activity steps. All are well supported.
    - Activity 1: Efficacy studies in a translational model of cardiometabolic HFpEF
    - Activity 2: Develop a clinical protocol synopsis and draft protocol for a Phase 1 human study
    - Activity 3: Prepare and conduct a pre-IND meeting with FDA
    - Activity 4: Conduct IND enabling studies
    - Activity 5: Finalize clinical protocol, consent form and investigators' brochure
    - Activity 6: Prepare and submit IND
- I have asked for extra clarification on the pig study design and the subject number/cohort in the first in human trial. Risks are clear - there is simplicity in the delivery and costs of goods look favourable. Formal analysis would be helpful.
- Well thought out study designs for proof of concept and proposed in vivo IND enabling toxicity studies. For toxicity study in pigs they should include all safety pharmacology endpoints (add CNS and respiratory); consideration of earlier time point for ECG assessment is also recommended.
- Will need to add standard battery of genotoxicity assays; hERG assay or rationale not to conduct. The studies may have been addressed/are being conducted in the monotherapy IND.
- Clinical protocol outline is sufficiently thought out for optimal pre-IND feedback.
- CMC feedback from previous pre-IND has informed readiness for GMP manufacturing.
- Well thought out, like that the IND will directly inform the combination.

Project Team and Resources

- An excellent team with deep experience in the translation from pre-clinical to clinical.
- Team has at its disposal all the relevant skills in development, clinical trials, manufacture, IND filing and so on.
- The team is excellent and is complemented with relevant consultants
- Experienced team with excellent resources.
- One key personnel is at 15% time and one wonders if other studies are funded and whether this, together with their current Director role and other roles, is feasible.

Population Impact

- Would have substantive impact locally and globally and in improving gender/ethnicity specific aspects of HF treatment. Impact has to come against the rapidly changing environment of HF therapies (small molecule

and otherwise) but there is clear need for innovative therapeutics.

- Diagnosis, demographics of disease burden and clinical presentation, current interventions including access and health outcomes clearly relevant to a California population are presented.
- Population impact could be very high.
- No plan for patient reported outcomes in the proposed trial.

Application #	PDEV-19150
Title (as written by the applicant)	A first-in-class CRISPR-CasX gene editor silencing APOC3 transcription for the treatment of Severe Hypertriglyceridemia
Therapeutic Candidate (as written by the applicant)	A novel gene editing therapy consisting of CRISPR-CasX mRNA and gRNA delivered via LNP to silence APOC3 gene and lower triglyceride levels
Indication (as written by the applicant)	Severe Hypertriglyceridemia (SHTG), in particular Familial Chylomicronemia Syndrome (FCS) and Multifactorial Chylomicronemia Syndrome (MCS)
Unmet Medical Need (as written by the applicant)	The proposed therapy addresses the unmet need for effective, lasting treatment of FCS and MCS by offering a single-dose gene editing therapy that can sustainably lower triglycerides, prevent acute pancreatitis, and reduce cardiovascular risks where current low-fat restrictive diets and drugs are ineffective.
Major Proposed Activities (as written by the applicant)	• Finalizing data package to evaluate potency, safety and efficacy • Preparation and conduct of a pre-IND meeting with the FDA • Completion of IND-enabling studies and preparation for IND submission
Statement of Benefit to California (as written by the applicant)	The proposed product is a first-in-class, single-dose gene editing therapy with potential for lifelong triglyceride reduction in FCS/MCS patients. The therapy can transform patients' lives, preventing, rather than treating, debilitating and deadly acute pancreatitis. It can lower ASCVD risk while eliminating high-cost chronic injections and restrictive diets. Development in CA creates high-value jobs, attracts investment, reduces healthcare costs, and advances the state's leadership in genetic medicine.
Funds Requested	$13,000,000
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: 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	89
Median	90
Standard Deviation	2
Highest	90
Lowest	85
Count	12
(85-100): Exceptional merit and warrants funding, if funds are available	12
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to

indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

Key Strengths and Weaknesses

- An in vivo editor is a truly transformative intervention.
- The project has a high value proposition. The applicants propose a novel gene editing therapy consisting of proprietary CasX mRNA, gRNA, and an LNP to silence hepatic transcription of APOC3 gene. The potential for this drug product to provide a meaningful and substantial improvement in clinical outcomes for the intended population is significant.
- Mitigation and contingency plans in the event of any "failures" during CMC phases of development are captured. The only caveat in the proposed plan is a lack of description of the delivery system which is critical for hepatocyte delivery. This was not adequately covered in the proposal. Clinical contingencies are adequately described.
- The value proposition was considered very high given the validated rationale and the potential to see an in vivo gene editor achieve success with a single treatment.
- This is a strong team, highly likely to succeed given the data to date.
- The strengths of this proposal significantly outweigh the weaknesses. The project addresses an important clinical problem, a critical barrier to progress in the field, and an urgent unmet medical need. The proposal is well written and the studies appropriately designed to achieve both early and late PDEV objectives within the proposed timeline and budget.
- Most notably, the biological target has been validated by successful RNAi and ASO therapies directed against the APOC3 gene as well as in certain individuals with genetic loss-of-function mutations in APOC3, and the potential for attaining IND clearance is significant. Other specific strengths include:
    - The studies are based on sound preliminary data in relevant mouse and non-human primate models.
    - An adequate body of data supports the potential feasibility of the studies, which include highly sophisticated, cutting-edge technology.
    - The gene therapy product is designed and manufactured to be more accessible and affordable compared to available treatments.
    - The proposed therapy is a single, one-time intravenous administration of the gene therapy drug over the lifetime of the patient.
    - Feasibility and practicality of the therapy's uptake by patients, caregivers and the healthcare system is substantial.
    - The proposal clearly details potential project risks along with clearly stated mitigation and contingency plans.
    - The leadership of the team is outstanding (both the PI and other members of the team). The investigators have complementary and integrated expertise and provide the necessary experience in biotechnology to achieve success at all levels.
    - The PI and team are knowledgeable about the clinical landscape and justification of the proposed technology to address certain unmet clinical diseases associated with severe hypertriglyceridemia.
    - The team has access to all necessary resources and facilities, including manufacturing facilities, to

successfully conduct the proposed activities.

- Minor weaknesses include: • The CMC plan lacks some detail of the analytical techniques that are included in the project. In particular, little information is provided on the design of the lipid nanoparticle (LNP) delivery system to the liver, and more specifically to hepatocytes. Why was the LDL receptor chosen for targeting of the STX-1400 therapeutic agent and not the asialoglycoprotein receptor, which is highly expressed only on hepatocytes? • Key regulatory strategies are only superficially described, including any preliminary discussion(s) with the FDA. • Greater patient engagement is somewhat lacking, and should be addressed in the short-term.
- The preclinical data are compelling and do not require another optimization campaign or round of changing the variant when the data are already strong. Feasibility is established, so there is no need for further product development and characterization. CIRM funding is not warranted for further lead optimization for four other variants.
- No regulatory advancements have been made considering significant data presented to support the target.
- The early activities involving another molecular engineering campaign do not seem necessary.

Value Proposition

- The applicants propose a novel gene editing therapy consisting of proprietary CasX mRNA, gRNA, and an LNP to silence hepatic transcription of APOC3 gene. The potential for this drug product to provide a meaningful and substantial improvement in clinical outcomes for the intended population is significant.
- The target disease is rare, but this approach has the potential to scale from several hundred FCS patients to thousands with MCS and millions with SHTG.
- The proposed product is a potentially curative single-dose therapy. There is one approved therapy that requires monthly injections, and one in development - both are described as requiring costly lifelong continuous treatment.
- The target is de-risked significantly given the other genomic medicine therapeutic programs in development.
- The proposed therapy is superior to current therapies for efficacy, safety, and most notably patient burden. It is promoted as a single, one time dose administration for the life of the patient. The expected impact of addressing the unmet medical needs for this population of patients is significant, as well as caregivers and the healthcare system in general.
- The PI provides detailed and clearly stated justification for the development of this drug product. The drug product (a gene therapy) is designed and manufactured to be more accessible and affordable compared to available treatments or therapeutics currently in clinical development for the intended patient population and healthcare system. Affordability for the long term is significantly greater compared to available treatments, as well as those in other clinical trials. This in part, is due to the fact that the product is administered once as a single intravenous dose for permanent reduction in APOC3 gene expression.
- The feasibility and practicality of the therapy's uptake by patients, caregivers and the healthcare system is substantial. The product is designed to be administered as a single intravenous dose for the life of the patient. This is in contrast to current therapies that require repetitive dosing to lower triglyceride levels. This would result in a substantial advantage for the patient, and a significant reduction in medical costs over their lifetime.
- The therapy has a significant advantage to current therapies for safety and efficacy.

Rationale

- The rationale is strong and supported by clinical data.

- The preclinical 'prototype' data are strong, but so far effects have only been tested <3 weeks.
- The nonclinical data set is compelling and adds to the scientific rationale around this therapy, offering strong potential for a successful IND.
- The nonclinical data are very strong and consistent with the rationale.
- The scientific rationale, including justification for the indication, therapeutic approach, and route of administration are robust, logical, and address an urgent unmet medical need. That said, refer to later comments on the LNP delivery system that is considered but poorly described.
- The proposed project addresses an important clinical problem and a critical barrier to progress in the field.
- The studies are based on sound preliminary data in relevant mouse and non-human primate (pre-clinical) models. The PI and his team provide compelling evidence of disease modifying activity.
- The rationale for the project is supported by an adequate body of data that support the potential feasibility of the studies, which include highly sophisticated, cutting edge technology.
- There are numerous strengths and only minor limitations of the data presented and the models which were utilized in the completed studies. The data generated in the rodent and non-human primate studies was statistically significant and supported the overall therapeutic value of the drug product. That said, it would have been helpful for the PI to also consider epigenetic off-site changes, in addition to those associated with modifications in gene sequence, as a potential limitation of the gene therapy.
- The proposal does an excellent job of considering potential problems and alternative approaches. What is limited, and somewhat surprisingly, is discussion of the delivery system. While it is stated that the delivery of cargo to hepatocytes is with an LNP, it is only in Figure 1 that shows that targeting of the complex is to the LDL receptor. This is somewhat surprising considering that most cells in the body express the LDL receptor. The delivery system is obviously key to efficient hepatocyte delivery and APOC3 gene reduction. Why was the asialoglycoprotein receptor not considered, which is only expressed on hepatocytes in extremely high numbers?
- The proposed therapy is a single, one time intravenous administration of the gene therapy drug. No discussion is considered on the persistence of the complex during hepatocyte replication, which albeit infrequent does occur during the lifetime of the patient.

Project Plan and Design

- It's not clear if the proposed $3 million model studies are truly necessary. CIRM should revisit the justification for these at the appropriate time.
- It's not clear why an INTERACT meeting is not planned until 2027. An earlier meeting could help the program.
- There are challenges in guide RNA CMC that have been properly noted. This is likely to be a key issue in making drug product.
- The proposed activities are necessary and appropriate to efficiently and effectively progress the project to IND clearance. The preclinical studies, IND-enabling studies, process and analytical development/testing, clinical protocol drafts and trial startup activities are stage-appropriate, clearly written and highly relevant to the success of the project.
- Both the early and late PDEV objectives will be achieved with the proposed budget and timeline, as outlined in the proposal. The proposed grant application clearly and in significant detail assess the validity of the potential project risks identified along with the mitigation and contingency plans presented. In addition, the PI and his team provide a logical and relevant description of how the proposed project, spanning 4-5 years, incorporates state-appropriate access and affordability planning to support future market access. That said, appropriate mitigation and contingency plans are discussed in detail for relevant risks, including lot failure of

GMP manufacturing and trial enrollment.

- The overall plan is well-designed and there is evidence of the potential to reverse course for this disease. Strong potential for all study objectives to be met within the proposed budget and timeline based on the proposed study plan.

Project Team and Resources

- A well-organized team was presented in the application with many collaborators, yet the application did not say much about the previous experience of the team members that might have been helpful to this application.
- This is an excellent team with deep experience.
- The leadership of the team is outstanding (both the PI and other members of the team). The investigators have complementary and integrated expertise and provide the necessary experience in biotechnology to achieve success at all levels. Of note, the PI is highly qualified to lead the project; and together with the myriad of other team members have designed an important, highly feasible approach that includes appropriate governance and organizational structure for the project.
- The team's leadership, expertise and staffing plan are appropriate to successfully navigate the project to IND clearance. This includes expertise and staffing relevant to the areas of non-clinical, GMP manufacturing, analytical, regulatory and clinical safeguards. The PI has provided a highly robust plan for coordination and execution of the project over the indicated timeline.
- The team has access to all necessary resources and facilities, including manufacturing facilities, to successfully conduct the proposed activities. The descriptions provided are clearly written, and inclusive of potential problems and alternative approaches if certain resources and facilities do not become available.
- The collective team, including consultants and subcontractors, have a demonstrated an extensive track record of supporting stem cell-based and genetic therapy projects to clinical trials. There is expertise on the team that addresses every potential aspect of the project from early PDEV to late PDEV.
- Mitigation and contingency plans in the event of any "failures" during CMC phases of development are captured. The only caveat in the proposed plan is a lack of description of the delivery system which is critical for hepatocyte delivery. This was not adequately covered in the proposal. Clinical contingencies are adequately described.

Population Impact

- The applicant’s understanding and consideration of genetic, environmental and other external factors that may impact on the adoption, effectiveness or safety of the proposed therapy are clearly stated, relevant and entirely inclusive.
- The intended clinical study population in the context of the project stage and current knowledge of demographic groups at risk for the target indication are appropriate for the proposed studies. At least three (3) separate patient populations are discussed in detail and appropriate for the target drug product.
- This reviewer can only assume that the applicant’s prior or proposed activities incorporate perspectives and experience from patients and individuals affected by the target indication, i.e., those with significantly elevated levels of triglycerides and associated co-morbidities.
- The proposal outlines a critical disparity in health equity affecting Hispanic groups in California.

Application #	PDEV-19140
Title (as written by the applicant)	CRISPR/Cas9-mediated gene editing of hematopoietic stem and progenitor cells for Friedreich's ataxia (FRDA)
Therapeutic Candidate (as written by the applicant)	Autologous CD34+ HSPC collected from Friedreich's ataxia (FRDA) patients and edited ex vivo using CRISPR/Cas9 to remove the GAA repeat expansion in intron 1 of frataxin (FXN)
Indication (as written by the applicant)	Friedreich's ataxia (FRDA)
Unmet Medical Need (as written by the applicant)	Friedreich's ataxia (FRFDA) is an autosomal recessive, multi-systemic, neurodegenerative disease with a prevalence of 1:50,000. Our therapeutic candidate offers the potential for a one-time, life-long intervention that addresses the multi-systemic manifestations of the disease.
Major Proposed Activities (as written by the applicant)	• Completion of IND-enabling studies: in vivo toxicology, manufacturing validation, pharmacology, and in vitro safety studies • Clinical protocol development and implementing infrastructure and documentation for trial initiation • Prepare and submit IND application
Statement of Benefit to California (as written by the applicant)	FDA's approval of Skyclarys marked the first disease-modifying therapy for Friedreich's ataxia but offers only modest benefit by slowing, not halting, neurologic and cardiac decline. It does not address the root cause, frataxin deficiency, thus requiring lifelong administration to sustain effect and creating substantial financial burdens for families and California's Medi-Cal. This underscores an urgent need for one-time, curative treatment delivering significant clinical outcomes and long-term economic value.
Funds Requested	$7,423,504
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: 88

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	88
Standard Deviation	4
Highest	95
Lowest	75
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	12
(1-84): Not recommended for funding	2

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

Key Strengths and Weaknesses

- Strengths: (a) Demonstration of significant improvement in the humanized mouse model of Friedreich's ataxia (FRDA). (b) The PI has experience with this strategy in cystinosis, using the same strategy (which is in phase I/II). (c) Potential for lifelong microglial supply from seeding of bone marrow / spleen / thymus. (d) Strategy should work for all FRDA patients.

- Weaknesses:

  (a) Low level seeding of CNS and peripheral tissues (<5%) – and uncertainty about impact on deep cerebellar nuclei and other structures.

  (b) It would have been helpful to have included an FRDA specialist clinician on the team.

- The applicant has put together a compelling proposal. The scientific rationale is sound, the team has experience with this modality and has addressed regulatory feedback sufficiently to warrant additional funding for late stage pre-clinical activities.

- Risks in this approach are two-fold: (1) the strategy requires high efficiency and fidelity across gene editing, cell migration, differentiation, and frataxin expression and diffusion; and (2) consistent manufacturing of autologous gene-edited HSPCs is complex, difficult to standardize, and expensive. Sustainability challenges have been seen across the industry, but these approaches should still be supported. The combination of preclinical and CMC activities proposed is designed to address these risks.

- Project Plan and Design: CMC activities are generally well-designed to enable IND submission and success with the FDA review. Three issues of concern: 1) sgRNA acceptance criterion is lower than FDA suggested (sponsor must provide justification); 2) proposed potency assay is not a functional assay; 3) FDA wants to see the CFU assay as a defined lot release criterion with specific acceptance criteria defined for erythroid and myeloid lineages. The current activity suggests that the CFU assay will be an additional characterization assay with results reported, but no defined acceptance criteria.

- The investigator has a lot of experience in this area - they developed the technology have demonstrated success with the same autologous cell/CRISPR approach in another indication (same author). The therapy has the potential to produce a life-long source of cells due to continuous production after transplantation.

- The proposal incorporates strong evidence despite the number of steps that have to happen to have a clinical effect.

- There is a concern that 5% seeding will not be sufficient to cause an effect, even with nonclinical supporting data in humanized mice.

- The complexity of CFU testing could be rate-limiting. The potency assay is not rate-limiting for the IND but needs a functional assay upon further discussion with FDA to get to a functional outcome.

- The complexity of CMC is a concern.

- Preclinical data are compelling and show the applicability of this CRISPR strategy in a humanized mouse model.

- For the trial the applicant plans to target patients aged >18 initially, and then lower to age 14 based on functionality. They may require a higher number of patients enrolled to establish efficacy, which is a future

regulatory concern.

Value Proposition

- Friedreich's ataxia is a rare, inherited neurodegenerative disorder caused by frataxin deficiency. This deficiency leads to Nrf2 dysregulation and progressive neurological decline, creating substantial burden for patients, caregivers, and healthcare systems. A single treatment with curative potential would address a significant unmet medical need.
- Friedreich's ataxia is a significant unmet medical need as there is no cure and only a single approved drug that treats symptoms.
- The value proposition is that there is no cure, and the only approved therapy treats symptoms rather than the underlying disease. This is a personalized medicine that carries procedural risks (HSPC mobilization, leukapheresis for 3–4 days, and myeloablative conditioning). However, the potential for a one-time curative treatment may outweigh these risks.
- The unmet medical need is high. The currently approved drug (Biogen's Skyclarys) only modestly slows progression. Rational, frataxin-replenishing therapies are needed. This novel cell-based strategy represents one such modality.
- There is currently a single approved drug for Friedreich's ataxia (FRDA), which will alleviate symptoms but does not prevent progression. The life expectancy for individuals with FRDA is around 40-50 years, with increasing complications, including heart disease. The possibility that a single treatment would provide life-long intervention would provide a meaningful and substantial improvement in clinical outcomes.
- This is a novel modality to replenish deficient frataxin in FRDA. Autologous HSPCs are mobilized, engineered ex vivo via CRISPR to remove the expanded GAA repeat, and transplanted following myeloablation. The PI has demonstrated seeding of modified microglia into peripheral and CNS tissues with evidence of mitochondrial transfer and behavioral and structural improvements in a humanized mouse model.
- This approach is likely to have beneficial impact in both systemic and CNS compartments.
- There is high unmet need due to the lack of treatments that restore function. The therapy described directly addresses the root cause of the disease and its pathology.
- Rare diseases have historically been difficult to commercialize solely in the private sector. The public-private partnership aspect of this application is appealing for developing potentially curative treatments in diseases with high unmet need.
- Even if the scientific approach is successful, the small addressable patient population represents a significant risk. Although the applicant notes partnership interest from two pharmaceutical companies, additional partnerships with rare-disease-focused groups (like the Rare Disease subunit of Chiesi group) could be considered.
- A gene-modified ex vivo cell therapy won't be more accessible than an orally available medicine such as Skyclarys. However, given the potential for a one-time curative treatment and the potential reduction in disease burden and lifetime cost, this therapeutic approach is worth developing, especially compared to outcomes with the current standard of care.
- As autologous gene-modified cell therapies such as Casgevy and CD19-targeted products like Kymriah, Yescarta, and Tecartus gain greater clinical uptake, advances in treatment center infrastructure, payer procedures, myeloablative protocols, and patient community acceptance will benefit this entire therapeutic class, including the one proposed here.
- Risks in this approach are two-fold: (1) the strategy requires high efficiency and fidelity across gene editing, cell migration, differentiation, and frataxin expression and diffusion; and (2) consistent manufacturing of autologous gene-edited HSPCs is complex, difficult to standardize, and expensive. Sustainability challenges

have been seen across the industry, but these approaches should still be supported. The combination of preclinical and CMC activities proposed is designed to address these risks.

- Currently, two gene therapy products in clinical trials use AAV to deliver a functional frataxin gene. However, an autologous cell therapy approach may offer safety and efficacy advantages over AAV-based strategies.
- Two other gene therapy products in development use AAV to deliver functional FXN. Solid Biosciences' AAV product is administered via intradentate nucleus and intravenous routes, while Lexeo/Weill Cornell's product targets cardiomyopathy via IV infusion. The applicant proposes an autologous personalized approach requiring stem cell mobilization, leukapheresis, ex vivo CRISPR editing, and myeloablation. This therapy would need to demonstrate superior safety and efficacy to compete with AAV-based therapies, should those also be successful.
- The feasibility and practicality of this therapy's uptake by patients, caregivers, and the healthcare system will be dependent on the cost savings relative to chronic care and on the long-term efficacy and safety.
- The proposal includes substantial partnership with patient advocacy organizations to identify, educate, and recruit FRDA patients.
- Pricing, affordability, and the risk profile are likely comparable to other competing biologics in this space.
- The investigator and their spin-off company have developed key patent protections and are in discussions with larger companies regarding potential partnership. These activities support financial sustainability necessary for long-term therapeutic development.

Rationale

- The proposed mechanism of action is restored expression of frataxin in differentiated HSPC progeny (such as macrophages and microglia), along with transfer of frataxin-containing mitochondria from donor cells into affected tissues, including neurons and potentially cardiomyocytes and skeletal muscle. This presents scientific risk due to the inability to directly modify the major affected cell types; however, the multisystem etiology of FRDA makes alternative direct approaches extremely difficult. There is also general evidence supporting trafficking of differentiated donor HSCs to the CNS, and the applicant has demonstrated disease modification in the mouse model.
- There is demonstration of significant improvement in the humanized mouse model of FRDA. The humanized mouse model, while appropriate for testing CRISPR correction, has a mild phenotype compared with the human condition (as acknowledged) and does not fully allow appreciation of phenotypic correction, especially cardiac, which could be an important impact of this therapy.
- Regarding CNS improvement: (a) Despite phenotypic improvement in the humanized mouse, it is unclear if the low-level seeding of CNS and peripheral tissues will impact the deep cerebellar nuclei and other relevant structures. However, the value of peripheral correction (metabolic, cardiac) should not be underestimated. (b) There is potential for lifelong microglial supply from seeding in bone marrow, spleen, and thymus, which was much higher.
- CRISPR correction rates are 20–50%, so only a proportion of microglial seeding is expected to be potentially transformative.
- Editing efficiency with electroporation enhancement was notably higher in human non-FRDA PBMCs as compared to humanized mouse PBMCs. This may reflect heterochromatin access in primary cells versus transformed cells.
- The risk of CRISPR off-target is low – but present – and low-levels of somatic cells with off-target effects may not be detectable.
- There is risk due to lack of clinical experience with tolerability of myeloablation and HSPC/bone marrow

transplantation in the FRDA population.

- The PI has experience with this strategy in cystinosis - a distinct strength.
- The editing strategy is a dual double-strand break approach to excise the GAA expansion. This is the only approach that can directly remove a genomic repeat region of this size.
- As noted above, the platform for ex vivo gene-modified blood cells has been established by precedents such as Casgevy and autologous CAR-T cell therapies. Many learnings from those therapies are recapitulated here, to the applicant's strength.
- The proposed therapy is based on the understanding that the very high number of GAA repeats in intron 1 inhibits transcription of frataxin mRNA. Gene editing to remove the GAA repeats is expected to increase transcription. The therapy uses mobilized HSPCs with the expectation that these cells will differentiate into microglia and macrophages, and that expressed frataxin will reach affected neurons and myocytes via mitochondrial transfer.
- The investigators have performed studies in multiple murine models, in vitro co-culture systems (to demonstrate mitochondrial transfer), and in mobilized CD34+ cells from five FRDA patients to support the proposed mechanism of action. These studies are relevant, well-designed, and provide robust supporting data.
- The proposed therapy rationale is that frataxin mRNA expression is diminished due to the expanded GAA repeats in intron 1. Removing the repeats via gene editing is expected to increase frataxin expression and inhibit neurodegeneration. Gene editing is conducted in mobilized HSPCs that differentiate into microglia and macrophages, enabling delivery of frataxin to deficient neurons via mitochondrial transfer.
- Several proof-of-concept studies have been conducted in murine models, in vitro systems, and mobilized CD34+ cells from five FRDA patients to assess mitochondrial transfer efficacy. These studies are relevant, well-designed, and support the scientific rationale.
- The scientific rationale is sound. Developing drugs for rare diseases can provide regulatory advantages, and diseases resulting from a single-gene defect are strong candidates for gene therapy. The route of administration is a single IV infusion, which is widely accessible.
- Diseases due to a single-gene defect are excellent targets for drug development. The preclinical data show that the corrected gene product is produced at clinically relevant levels in the disease mouse model.
- The applicant used a Friedreich's ataxia mouse model and showed that correction of the genetic defect permitted production of functional frataxin protein.

Project Plan and Design

- This is a Late PDEV proposal, which is well-aligned with FDA type B.
- The PI's experience with the cystinosis program is a strength in moving this project along.
- Much of the correspondence with the FDA concerned the off-target and toxicology assays. In particular, the FDA had asked the sponsor to conduct an unbiased, genome wide assessment of integration of the electroporation enhancer. The sponsor provided details on this assay in response to a question. The assay described comes from a strong group with a long track record of high quality work in the CRISPR space. Nonetheless, I will share some considerations that could be important for good data quality.
    - First, though the applicant notes the electroporation enhancer should be rapidly degraded, a sample treated with exonuclease I to degrade any remaining enhancer prior to the UNCOVER-Seq protocol could be useful to eliminate any signal coming from free/unintegrated enhancer.
    - Second, as integration events are expected to be low frequency, it is critical that enough cells from the manufacturing runs are used for this assay and are sequenced with enough depth to give

statistical power to any findings. The scale of the manufacturing was not stated, nor were the cell number needs for the other assays from this run. The team should do the math and power analysis to determine the appropriate manufacturing scale to ensure enough cells to sufficiently power all assays.

- It's unclear if the long term stability studies of the final drug product out to 18 months are necessary. As noted in the application, this length of time is far longer than expected for treatment. This reviewer could not find the quote referenced for the cost of this long term stability study, but perhaps reducing the time points could help reduce the project time and cost.

- Generally, the CMC activities are designed to address many of the issues raised by FDA in the pre-IND meeting. In particular, the major CMC activities proposed address the critical FDA comments from the pre-IND meeting: generation of engineering-grade/GMP grade reagents; GMP manufacturing runs on CD34+ HSPCs with long-term stability testing; and development of a potency assay, A few specific notes below on where there may be some gaps between this reviewer's understanding of the FDA recommendations and what the investigators are proposing in regard to the CMC activities.

- There is a slight discrepancy between the pre-IND comments and the proposal on the AC for the sgRNA. A justification to FDA may be needed.

- CMC Activity 2B proposes to develop a potency assay. It's notable that the FDA's comment in response to the pre-IND package reminds the sponsor that a potency assay must assess the biological function of the product. The detection method proposed may not be viewed favorably by FDA as a potency assay. While this is not a rate-limiting step for starting the IND, it may become one at the later stages. This reviewer would encourage the investigators to discuss the proposed potency assay with FDA during the IND phase 1 clinical trial stage to get more guidance on the proposed assay.

- The description in the manufacturing plan synopsis does not seem to meet recommendations from the FDA's pre-IND review.

- The plan, if executed to it potential, including the development of a "functional" assay/potency, has the potential to lead to an IND within the timeframe.

- The investigators have had multiple meetings and communications with the FDA, and it is clear what additional preclinical and CMC/manufacturing activities must be completed for the IND.

- The proposed budget has very specific costs for preclinical and CMC activities, which are derived from actual quotes from the CMO/CROs that would be performing these activities. The objectives set forth for this grant, including completing additional preclinical studies, manufacture of the product, preparing and submitting the IND, and preparing for clinical start-up up should be feasible with this budget.

- The risks to achieving objectives have been mitigated by the extensive meetings and correspondence with the FDA.

- The applicant has requested funds for access and affordability planning and for market landscape analysis.

Project Team and Resources

- The PI is well qualified to lead this project. The PI's experience with the biology of this procedure – and in already shepherding a previous indication through this type of pipeline – are major strengths.

- The assembled team covers all relevant subspecialties (neuromuscular, cardiology, etc.).

- It would have been helpful to have included an FRDA specialist clinician on the team.

- The project team seems to have both the breadth and depth of experience necessary to drive this project to success. In particular, the prior experience of the applicant in first in human trials as well as the choice of regulatory consultant are encouraging. The team seems to be taking advantage of the robust network of

California-based manufacturing, development, and clinical infrastructure to advance their work.

- The PI is very experienced with gene therapy clinical trials, and with studies using ex vivo modified HS/PC in particular. The PI currently has an ongoing IND with the FDA to evaluate an ex vivo modified HS/PC approach to treat cystinosis. In addition, the PI is the Director of the institutional gene therapy institute, suggesting institutional recognition of her expertise and competence in performing these studies.
- The PI has a spin-off company that is providing up to $1M in contingency funding to support the proposed activities in this proposal.
- The PI has assembled a large number of competent investigators, and is leveraging expertise at a CIRM Alpha Clinic to ensure clinical and regulatory infrastructure are in place to support running a clinical trial, as well as a number of CROs.
- The team has the leadership, expertise, and staffing plan to successfully develop an effective IND. Much of the key non-clinical, GMP manufacturing, analytical, and regulatory work will be done by outside CMO/CROs with the appropriate expertise. This use of outside expertise is not uncommon for academic teams performing drug development.
- This project has a robust plan for execution of the project, which has been clearly outlined.
- The team has resources and facilities for manufacturing and testing, and has contracted with excellent CROs/CMOs to successfully complete the proposed activities.
- The collective team, as evidenced by the work completed to date, appears capable of moving this stem cell-based and genetic therapy project to a clinical trial.

Population Impact

- The application demonstrates thorough knowledge of the patient population, and, critically, includes a letter of support from a patient advocacy group.
- The primary driver of case severity correlates with the number of GAA repeats. This is apparently a factor that runs independent of any other factors, such as race and sex, although the case rate/fatality rate is predominantly in white patients.
- Given the large costs per year of treatment currently, successful intervention with this one-time therapy in these younger patients will not only improve the health outcomes of these children, but also reduce the financial burden over their lifetime of healthcare costs.
- The proposed clinical trial population will reflect the naturally occurring rates of case rate/fatality as derived from the FRDA natural history study. This seems like a reasonable and feasible approach.
- Friedreich's ataxia is a chronic condition, and because of the progressive nature of the disease and significant co-morbidities, there would be adoption of this therapy if it is shown to be safe and effective.
- The applicant team is very knowledgeable about this disease.
- This modality will theoretically work for everyone with FRDA, because all have at least one expanded GAA repeat. However, it is likely to work better in those who are homozygous for the expanded GAA repeat because correction rate is ~50%.

Application #	PDEV-19154
Title (as written by the applicant)	Late-stage development of [redacted therapeutic candidate], an UNC13A Targeting Antisense Oligonucleotide treatment for Amyotrophic Lateral Sclerosis, for IND-enabling studies
Therapeutic Candidate (as written by the applicant)	[redacted therapeutic candidate] is a genetic medicine that repairs faulty messages in ALS patients' nerve cells to restore protein function and protect movement.
Indication (as written by the applicant)	Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease is a fatal neurodegenerative disorder causing progressive paralysis and death.
Unmet Medical Need (as written by the applicant)	Approved disease-modifying treatments provide only modest benefit. Tofersen, an ASO targeting the SOD1 mutation only works for 2% of patients. UNC13A loss is a consequence of TDP-43 pathology that affects 97% of patients. Thus, [redacted therapeutic candidate] represents a therapeutic opportunity for nearly all patients.
Major Proposed Activities (as written by the applicant)	• Complete safety studies in animals to show [redacted therapeutic candidate name] is safe enough to begin human testing. • Produce [redacted therapeutic candidate] and placebo under Good Manufacturing Practice, the quality standard ensuring medicine is safe, pure, and consistent for clinical use. • Prepare and submit applications to U.S. and European regulators to begin the first-in-human Phase 1 clinical trial of [redacted therapeutic candidate name].
Statement of Benefit to California (as written by the applicant)	This project develops a new treatment for ALS, a fatal disease with limited options. Success will give California patients early access to a first-in-class therapy, create jobs through local clinical trial sites, and strengthen the state's leadership in neuroscience research. It will also expand collaborations with California universities and hospitals and promote health equity by including patients from diverse and underserved communities.
Funds Requested	$7,500,000
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	86
Median	87
Standard Deviation	2
Highest	87
Lowest	82
Count	12
(85-100): Exceptional merit and warrants funding, if funds are available	10
(1-84): Not recommended for funding	2

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

Key Strengths and Weaknesses

- Very good target, novel chemistry, huge unmet need. Other companies are several years ahead (potentially) but this is worth pursuing.
- Good target and plan but main issue preventing a fundable score is the fact that it is some time behind two other products that are already in or about to enter clinical trials.
- Key Strengths - strongly supports value proposition; validated target; good supporting data; novel chemistry may support better product performance.
- Key Weaknesses - limited details on clinical operations planning and readiness; BfArM feedback not yet complete; project plan unclear on mixing of DS batches.

Value Proposition

- If effective in the broad TDP-43 (TAR DNA-binding protein 43) ALS population, this could lower downstream utilization (respiratory failure interventions, PEG dependence, long hospitalizations) and caregiver load; however, these are projected benefits contingent on clinical efficacy.
- The program emphasizes established clinic workflows (lumbar puncture; no specialized infrastructure) and fully synthetic, scalable phosphoramidite SPS - both supportive of broader access and favorable COGS vs. complex biologics/viral vectors, pending final pricing.
- The plan maps a multi-site cGMP chain with QA/QP oversight and traceable qualified starting materials - supportive of reliable scale-up, though tech-transfer and global QA releases are critical execution risks pre-commercial.
- Potential to provide meaningful and substantial improvement in clinical outcomes is evidenced by the possibility of restoration of synaptic function, leading to delay in onset/suppression of and progression of ALS symptoms.
- Expected impact of addressing unmet medical need is substantial - once onset occurs, ALS patients rapidly require 24/7 care therefore to reduce those needs by extending the ability to function independently, would preserve patient quality of life/ADLs, delay/decrease care burden on caregivers and reduce overall cost to healthcare system.
- Accessibility and affordability of this ASO should be comparable or better to existing ASO pay structures for other approved therapies and may benefit from economies of production scale, given the larger target patient population.
- The feasibility and practicality of uptake compared to standard of care will likely be good - the mechanism for protein restoration may be suitable for a vast percentage of the afflicted patient population and therefore attractive to patients and caregivers that can't benefit from targeted genetic treatment nor have seen benefit from other approved therapies. Suspect the healthcare system will be circumspect about the patient population eligible for treatment, relying heavily on the clinical outcomes however, given the severity of the disease, will consider the practical aspects of ROI treatment vs progressively higher costs/requirements for

physical care.

- Very important.

Rationale

- In human iPSC-derived neurons with TDP-43 depletion, [redacted therapeutic candidate] restores synaptic UNC13A protein and fully rescues spontaneous and network glutamatergic activity (iGluSnFR), indicating functional reversal downstream of the splice correction.
- Extremely good rationale.
- The UNC13A cryptic exon is “not faithfully modeled in rodents,” so efficacy relies heavily on human iPSC systems; while translationally compelling, confirmation in patients is essential. Biomarker/assay work (UNC13A RNA/protein in CSF/plasma) is ongoing and currently faces sensitivity/reagent gaps—adding risk to PD readouts early in clinical development.
- The genetic rationale + human neuron functional rescue + large animal model exposure/safety form a coherent chain from target to organism, with IT feasibility supported; key residual risks are the lack of a fully faithful animal efficacy model and incomplete biomarker toolkit, which could complicate early proof-of-mechanism despite a strong mechanistic foundation.
- Scientific rationale is sound and based on the understanding of impact from depletion/displacement of TDP-43 from neuronal nuclei to neuronal cytoplasm, effectively removing TDP-43 from performing its key regulatory role in RNA metabolism of repressing cryptic exon inclusion. Inclusion of the cryptic exon leads to UNC13A mRNA decay, which subsequently cannot be translated into UNC13A protein - no protein = no to very limited synaptic function.
- Animal models used are appropriate and relevant to understanding efficacy and safety. Available data is based on *in vitro* assessments and *in vivo* models. In *In vitro*, iPSC-derived h-neuronal test system, hUNC13A mini-gene model, orthologous KO mice, purpose-built hUNC13A (knock in) mice, C57/BL6 mice, Sprague-Dawley rats, patient-derived neuronal cell lines, iPSC derived motor neurons and large animal models have/are contributing preliminary PK/PD, safety and efficacy insights to the program design.
- Underpinned by GWAS identification, the identified SNP is broadly common to ALS patients where cryptic exon suppression is observed, facilitating selecting patients that have lost TDP-43 function (~97% of ALS patients exhibit aggregation of TDP-43 protein in the cytoplasm (nucleic depletion)).

Project Plan and Design

- GLP/nonGLP studies required for filing the IND (FDA feedback is being addressed in animal studies, Ames Testing, DDI) are in place/will be conducted, manufacturing and packaging of GMP compliant DP and Placebo/Diluent are required for initiating the Phase 1 clinical study.
- Excellent project plan and design.
- Agree with regulatory designations to be pursued – Fast Track, Orphan, and at the right time, BTD and PRIME. Assuming good safety and early efficacy outcomes, these designations set the stage for seeking accelerated approval and conditional marketing authorization. Use of European facilities for manufacturing and QP release will also be able to serve the US market.
- Planning for up to 6 domestic and international clinical sites, will establish a footprint/ foundation that facilitates expansion to later stage clinical study, assuming positive data.
- The PDEV plan is proportionate in scope and rigor for IND readiness, with well-defined CMC, tox, and regulatory milestones and clear risk containment. The only moderate vulnerability lies in the parallel complexity of analytical qualification and biomarker validation, which - if delayed - could compress the

regulatory buffer before IND filing.

- It is not unusual for IND prep and filing to take up to 6 months, assuming all data is available - project plan appears to provide only three months time for preparation to filing.
- BfArM scientific advice has not been completed therefore it's unknown what feedback/changes will be required to achieve clearance and start clinical study. The stated goal is to have at least three trial sites open (with diverse geographic coverage), which appears dependent on a successful CTIS process.
- The project plan describes "GMP-grade DS in two runs" combined into one batch of DS for clinical supply. Mixing of GMP runs into 1 batch (pg 32, Proposal) is not disclosed in the FDA briefing book. Its unclear what testing will be performed before pooling therefore this step may create an IND regulatory review risk.
- Clinical operational readiness has limited details on which sites, which vendors, etc. will be used (also unclear whether accessing the UK for CTA (IRAS) or filing under only CTIS for EU). Clinical site contracting can be challenging, taking longer than planned. It seems FDA has not seen the complete clinical protocol, only a synopsis in the briefing book. Additional questions may arise once the complete protocol is submitted in the IND.
- Risk #1 (pg 64 proposal) - two engineering runs to derisk GMP runs for DS appears reasonable. As noted, not clear what the pooling strategy is to obtain a GMP-compliant DS. The DP Placebo batch being made before the [redacted therapeutic candidate] DP batch is not a de-risking step since Placebo is exactly the same quality processing (minus active) as [redacted therapeutic candidate] DP. DP manufacturing should be de-risked via satisfactory APS (which is not mentioned). Presumably, the fill process/vial size fits within the APS brackets.

Project Team and Resources

- Team leadership is appropriate for preclinical. Early CMC, with heavy reliance on experienced mfg vendors, is likely satisfactory. Later stage CMC/development will require deeper resourcing. Its unclear there is sufficient clinical operations expertise to efficiently identify and activate clinical study sites and then follow through on routine management (given no CRO is identified). It seems a choice by necessity for a business CEO (instead of an MD/CMO) to be listed as a Principal Investigator- presumably he will be sufficiently advised by staff / consultants.
- The team has secured established GMP manufacturing partners—three facilities across Frankfurt, Italy, and EU—each with Phase 1–3 oligonucleotide experience, validated QA systems, and qualified personnel (e.g., QPs for EU release). These facilities collectively cover synthesis, fill-finish, packaging, and GDP distribution, ensuring end-to-end IND supply capability.
- Superb project team and resources.
- Collectively, the team and subcontractors have a proven track record across >50 oligonucleotide programs from discovery to clinic, supporting confidence in execution. The remaining moderate risk lies in applicants' still-developing internal QA/QMS capacity, which, while under establishment, must be stress-tested during the IND build phase to maintain compliance continuity.
- Regarding robustness of the plan, preclinical is well-defined, CMC is adequately defined (Quality unclear since QMS is in process of being built), Program/Project Management is in place, Clinical Operations outline identifies the correct activities. Applicant organization size suggests there may be bandwidth constraints.
- CMC vendors are appropriate, TBD for CRO capabilities. applicant does not have a complete QMS and will need a phase-appropriate system in place at IND filing.
- The potential for the collective team to perform this work is present - chemistry is strong, preclinical is relevant, CMC vendors are experienced and suitable, consultants/contractors for CMC and quality bring needed expertise, clinical operations execution skills unclear.

Population Impact

- The applicant shows a comprehensive grasp of genetic and environmental variability, articulates inclusive yet biologically grounded enrollment criteria, and meaningfully incorporates patient voices. The main area for enhancement would be operationalizing outreach to historically under-represented groups to ensure that inclusive intent translates into proportional trial participation.

- Applicant understands the medical/treatment landscape and recognizes potential hurdles such as price, accessibility and accessing impacted populations.

- Intended clinical study population is consistent with expected mechanism of action, excluding patients likely to not benefit.

- Applicant has previously obtained CIRM funding for preclinical activities and this proposal leverages those activities to enter clinic. Providing a disease modifying therapy that overcomes a known defective cell metabolic process leads to a sound, restorative approach. The applicant clearly understands the limitations of currently approved treatments and provides a robust solution to ameliorate disease symptoms, ideally delaying onset of debilitation.

Application #	PDEV-19133
Title (as written by the applicant)	Stem Cell-Based Cartilage Tissue Regeneration
Therapeutic Candidate (as written by the applicant)	Stem cell derived cartilage tissue implants
Indication (as written by the applicant)	A chronic cartilage lesion of the knee joint in patients younger than 55 years of age in whom traditional total joint replacement is not indicated.
Unmet Medical Need (as written by the applicant)	Osteoarthritis affects over 30 million Americans with an economic burden of $200B/year. There are effective therapies approved by the FDA. There is a significant unmet need for therapy to repair knee lesions, prevent osteoarthritis, and reduce the need for joint replacement.
Major Proposed Activities (as written by the applicant)	• Generate cell banks and tissue engineered implants for in vivo and in vitro testing • Conduct animal studies for in vivo proof of concept of biological activity and safety • Submit an IND package to the FDA
Statement of Benefit to California (as written by the applicant)	Annually, a signicant number of Californians sustain joint injuries that result in loss of cartilage and bone in the knee, are challenging to repair, and often lead to early osteoarthritis. There is no FDA-approved treatment that can change the progress of osteoarthritis. Nearly 50,000 joints are replaced every year in CA alone. Our therapeutic candidate, if successful in repairing lost tissue due to joint injuries, is likely to significantly reduce the need for joint replacement.
Funds Requested	$12,715,000
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: 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	86
Median	85
Standard Deviation	2
Highest	90
Lowest	85
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	14
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

Key Strengths and Weaknesses

- Exciting area. There are some concerns about chemistry, manufacturing and controls (CMC). The starting material may be variable, and therefore, this poses a risk from the outset of the project timeline. What the applicant needs to do manufacturing wise appears optimistic.
- Some timeline issues.
- Key Strengths

  - mechanism of action is reparative and restorative

  - FDA feedback is supportive and actionable

  - there's a sufficient project plan and positive CMC improvements.
- Weaknesses

  - extensive CMC work is needed prior to filing IND and treating patients

  - minimal preclinical work has been conducted with the new cell line to be taken forward.
- Strong team and preliminary data.
- Manufacturing strategy, specifically for cell line manufacture, cryopreservation, and whether the process will use scale up or scale out to make adequate material require additional detail and preliminary data.
- Extensive tech transfer is likely required with an unclear timeline.
- The tech transfer and manufacturing processes need to be better outlined and defined. Protocols are not complete. Selection of a scale out vs scale up manufacturing approach is unclear. Optimistic timeline.

Value Proposition

- This therapy addresses an unmet need of a pervasive condition with a technology that is seemingly less burdensome to utilize and more effective than current treatments.
- The potential for meaningful and substantial improvement in clinical outcomes is exhibited by the preclinical data showing cartilage embedment.
- Affordability off this off the shelf, single surgical intervention could potentially be on par with, or lower than, currently available implanted cell product costs.
- Assuming positive clinical data on regeneration, reduction or elimination of pain and return to baseline physical activity are achieved, uptake could be promising compared to the standard of care, microfracture surgery.
- A therapy that is feasible and cost effective to mitigate the development of OA and avoid subsequent

surgery would be welcome by patients utilized by patients.

- Treatment could enable broad patient access and uptake if manufacturing cost is managed.
- Applicants demonstrate successful implantation and cartilage restoration without inflammatory response or documented teratoma.
- Addresses an unmet need for durable cartilage regeneration beyond current available cell therapies. The therapy is intended to reduce OA progression and delay joint replacement, offering a single-surgery, off-the-shelf implant. The allogeneic, xenobiotic-free platform improves scalability and reduces cost.
- The current manufacturing process is complex and expected to incur high costs, especially regarding conjugation and final drug substance and drug product production.
- It's unclear if the current process is cost-effective. Licensing terms for hPSC are not defined, and market analysis is not yet performed. The latter is included as part of project scope.

Rationale

- Scientific rationale is sound. The product is an engineered "patch" that is potentially immediately beneficial upon implant. Preclinical data demonstrate repair of osteochondral defects. Mechanism of action suggests durability.
- The applicant's patch strategy is sound.
- Animal data from the new cell line is limited. Additional animal studies will be useful to confirm this cell line's performance. Relevant animal models have been used and are proposed for further studies.
- The preliminary data provided by the applicant demonstrates a strong scientific rationale for the proposed study.
- An evaluation of teratoma and tumorigenicity of the stem cell therapy is a strength of the application.
- Differentiation processes from PSCs to MSCs to chondrocytes are well established and demonstrated in chosen hPSC line.
- Strong supporting data and safety profile in animal models.
- Applicants were responsive to prior FDA feedback regarding the starting material and scaffold used to manufacture the product.

Project Plan and Design

- The applicants have had a good INTERACT meeting. The timeline is optimistic, and the cell line needs to be tested more.
- Proposed animal studies are IND-enabling. Engagement of experienced CMC resources for clinical manufacturing is stage-appropriate.
- Obtaining safety, dosing and efficacy signals from the animal studies should be achievable.
- Moving to a GMP-compliant manufacturing facility is necessary to initiate clinical manufacturing. There are many activities required to be GMP manufacturing ready. Timing to complete these tasks is likely underestimated, particularly for tasks such as upgrading raw material grades, qualifying new supplies, and deciding whether to use the very different technologies involved in scale up vs scale out.
- The proposed small and large OA models were selected to comply with FDA guidance.

- Given that 62% of women develop OA, and this sex disparity increases after age 50, consideration should be given to the sex of the animals evaluated in the preclinical studies.
- The plans to mitigate potential risks and associated costs (to be covered by the applicant) appear to be adequate for this proposal.
- Stage-appropriate access and affordability planning is provided in the application.
- The application provides comprehensive IND-enabling plans with large animal studies, GMP transfer to appropriate facility, and a clinical protocol.
- The current manufacturing process requires significant tech transfer to produce the therapy in the chosen facility.
- Comparability studies are needed for some key raw materials.
- PSC manufacturing protocols are incomplete and require optimization of variables such as seeding density. This is especially important for transition to CellStack/Hyperflask (for scale out) and stirred tank bioreactors (for scale up). Pilot studies demonstrating that scale out or scale up can generate sufficient material would strengthen the project. Note that expansion of MSCs in bioreactors requires identification and validation of the microcarriers to be used.
- Cryopreservation is vital for final product delivery, but it has not yet been optimized for the manufacturing process. Post-thaw yield and functionality data will help refine the scale out or scale up manufacturing workflow and ensure sufficient capacity.
- The timeline is feasible but highly contingent upon tech transfer and CMC process optimization.

Project Team and Resources

- Team leadership has appropriate expertise to execute animal studies, early phase clinical manufacturing and clinical operations. Team is acting upon FDA feedback in executing their project plan.
- Strong team.
- The transdisciplinary research team is well qualified to carry out the proposed investigation.
- The resources and environment are outstanding.
- Team is appropriate with proven track record.
- Strong institutional support.
- Manufacturing team is capable. They may require additional resources pending process optimization success.
- The team have a demonstrated track record in IND-enabling work (under prior CIRM awards), access to core facilities and GMP manufacturing partners. Regulatory experience and CMC strategy are validated by external experts.

Population Impact

- The clinical study patient population appears aligned with the anticipated commercial population (who would otherwise be treated with standard of care).
- The two year study duration may not be long enough to detect efficacy with significance; microfracture efficacy peaks at 2 years and fails on average by 4 years. However, 50% of microfracture patients do not

receive benefit after treatment, which should be detectable in the control group.

- No information was provided in the application of the impact of OA on women (62% of the cases), race/ethnicity (higher rates in Whites and Blacks), or income and education (1.5 times higher in individuals with lower income and fewer years of education). Applicants need to consider meeting with patients and members of the public to evaluate the uptake of this therapy.

- The focus on younger adults with focal knee lesions is a relevant patient population with unmet need and potential for long-term health benefits.

- There is no information provided regarding the population that will be impacted.

Application #	PDEV-19138
Title (as written by the applicant)	Noncoding RNA drug for arrhythmogenic cardiomyopathy
Therapeutic Candidate (as written by the applicant)	Therapeutic candidate is a synthetic chemically-modified RNA oligonucleotide.
Indication (as written by the applicant)	Arrhythmogenic cardiomyopathy (ACM), an inherited heart disease, is the leading cause of sudden cardiac death in young adults and athletes.
Unmet Medical Need (as written by the applicant)	ACM is a potentially lethal inherited heart disease, with an estimated prevalence ranging from 1 in 2,000 to 1 in 5,000 individuals worldwide, making ACM rare. ACM is a leading cause of sudden cardiac death in young adults and athletes. No current therapy has disease-modifying bioactivity.
Major Proposed Activities (as written by the applicant)	• Preparation and conduct of a pre-IND meeting with the FDA • Completion of IND-enabling studies • Prepare and submit IND for first-in-human studies of oral drug in healthy subjects and Clinical trial planning and start-up
Statement of Benefit to California (as written by the applicant)	ACM is a potentially lethal inherited heart disease, affecting approximately 10,000 Californians. Heart failure is also a complication. No current therapy has disease-modifying bioactivity. Our work seeks to develop a new, orally-active drug that will halt or even reverse the progression of ACM, restoring health and life to affected Californians. The California-based drug development efforts will also provide jobs, strengthen our economy and further establish our state as the leader in biotech.
Funds Requested	$10,419,929
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	86
Median	85
Standard Deviation	2
Highest	90
Lowest	85
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	14
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

Key Strengths and Weaknesses

- The proposed therapy is designed to target one of the underlying causes of Arrhythmogenic Cardiomyopathy. The disease affects young people and athletes resulting in potentially lethal outcomes with often no advanced warning, especially in patients who have not been genetically tested. The proposed therapy is designed to reduce cardiac inflammation by increasing macrophage efferocytosis, promoting clearance of interstitial debris and limiting chronic inflammation.The program is supported by strong proof of concept and safety in animal models and has been well-investigated.
- An orally bioavailable molecule would be accessible and low cost. Pilot data are strong.
- Strong clinical need. Bioinspired approach and FDA-aligned therapeutic with oral availabiliy. Excellent team and experience (especially with pre-FDA meeting with related product). Risk that the target is not as relevant in human as it is in mouse ACM models.
- The value proposition are: 1) Sudden cardiac death should be blunted or eliminated 2) Progression to heart failure could be much reduced 3) Fewer heart transplants would be required 4) Improved quality of life for patients--less impact on healthcare system and caregivers.
- Positive bioavailability in rodents with therapeutic activity. Strong CMC drug substance and drug product proposal are key strengths.
- Borderline value proposition.

Value Proposition

- The proposed therapy is designed to target one of the underlying causes of Arrhythmogenic Cardiomyopathy that results in accumulated fibrofatty and inflammatory debris in the cardiac interstitium and causes significant cardiac inflammation. The value proposition is that there are currently no approved treatments that exhibits disease-modifying bioactivity. The current standard of care for ACM patients includes beta blockers, anti-arrhythmogenic drugs; defibrillator devices, such as pacemakers, and heart transplant which manage ACM symptoms but do not treat the underlying causes of chronic ACM. The current proposed therapy is designed to reduce cardiac inflammation by increasing macrophage efferocytosis, promoting clearance of interstitial debris and limiting chronic inflammation. The supporting nonclinical data are convincing.
- Patient population has significant need.
- ACM is a condition with substantive unmet clinical need, rare but not ultra rare. As an oral agent, it would be accessible and easily delivered and relatively low cost as the manufacture and distribution would be rather conventional and therefore cost-effective. Mechanism of action is different for this therapeutic compared to conventional/other treatments. Main comparator is AAV. Uptake would be straightforward. This is not a complex therapeutic, albeit it is a genetic therapy not a small molecule.
- In general, the proposed project seems reasonable to attempt and would create value if successful.
- Affordability and accessibility are not addressed well.

Rationale

- The rationale for this product is based on the premise that ACM patients suffer from fibrofatty deposition in the cardiac interstitium that increases cardiac inflammation. The premise is also that inflammation is considered a primary cause of myocyte destabilization. Macrophages are phagocytic cells that scavenge cellular debris, in a process called efferocytosis.

- Intravenous (IV) and oral formulations of the product test the hypothesis that it induces macrophage efferocytosis, promoting clearance of interstitial debris and limiting chronic inflammation and progression of fibrofatty scar. The generalized targeting of interstitial inflammatory debris may affect different forms of ACM where destabilization of other adhesion molecules is known.

- Both IV and oral forms of the drug reduces arrhythmogenic substrate and myocardial fibrosis in vivo in DSG2 mutant mice. Above and beyond halting disease progression, the drug appears to at least partly reverse established pathology. This study showed no signs of toxicity at the doses tested.

- Preliminary results using the product in the rat acute myocardial infarction model indicates that orally-formulated product exerts cardioprotective effects at least as potent as those of the tested parent molecule. Using a micellar formulation, bioactivity of oral product in a rat myocardial infarction (MI) model reduced infarct mass and lower levels of cTroponin were observed.

- In a rat sepsis model, reduced cardiac function (reduced fractional shortening and reduced LV internal diameter) and elevated bacterial count was observed followed by recovery of all parameters following IV drug. In a transgenic mouse model of ACM, the drug induced preservation of ejection fraction following IV administration.

- A total of 7 studies were conducted to assess the product in mice and rats, mostly the IV formulation. An ex vivo study showed, importantly, that the product increased macrophage efferocytosis in rat PCMBCs mediated by decreased cytokine IL6 expression.

- The product is an RNA oligonucleotide; it's structure conforms to well-established conventions for >16 FDA-approved ncRNA drugs but remains a first-in class proposition. The simplicity of the oral formulation, straightforward synthesis and cost to manufacture potentially add to the value proposition. If the nonclinical benefits translate clinically, this could be a ncRNA therapy that provides a translational path toward non-invasive, disease-modifying treatment for patients with inherited cardiomyopathies. It makes the assumption that all forms of ACM derive from fibrofatty scar generated from interstitial fibrosis and inflammation. More studies, proposed in the application intend to assess dose-ranging following oral and IV administration, including assessment of off-target effects, PK and toxicity studies in two species.

- The work is embedded in the former work on cardiosphere extracellular vesicles (EVs) and the non-coding RNA which they have made an analogue for which essentially phenocopies the data of the EVs in ACM models.

- Route of administration can be oral or IV. IV has been the route for the product being developed for heart failure but oral administration is the ultimate aim. Though there is risk that it is not as effective as IV there is some reassurance. There is a great deal of data in vivo and ex vivo is assays that assess macrophage efferocytosis (the mode of action) and in vivo in ACM (DGM mutant mice). The mechanism of action is to clear debris from the heart in the myocardium of ACM and have seen that doing this can prevent and (at least particularly) reverse disease. The data so far seem strong and much of the work is published with some in unpublished form.

- Oral bioavailability seems to be established in two rodent species which elicits the desired therapeutic response. Proposed formulation approach seems reasonable. Proposed route of synthesis for RNA drug substance is reasonable and established. Proposed control of drug substance seems reasonable at a high level. Applicant proposes to add a second test of drug substance identity (next generation sequencing) for release testing as suggested by FDA at a pre-IND meeting. Drug product methods and controls appear to be adequate for intended use.

- The models used are relevant - it is unclear if the effect is specific to DGM-/- mice or could be in other forms of ACM mediated by other mutations. I did not see effects in an in vitro organoid model, for example, where one could include patient cells for reassurance that the drug works (or can work with a marker assessed) in

human samples, or are such models not available replicate the complexity in ACM?

- Strong rationale.

Project Plan and Design

- The project plan is a necessary extension from where the team are now: To include essential bio distribution and efficacy data with oral product; to develop the manufacture processes and to ensure FDA discussions and trial design for the first in human trial, which is the endpoint of this program. It is clear the PDEV objective can be met if successful. There will be a lot of key decision points and some assays need to be developed and many potential risks. The risks seem to be largely well defined and mitigated. Some reassurance is given with the prior discussions with the FDA on another product being developed for another indication under the same FDA program.

- Strong project plan.

- Proposed plans appear to be phase - appropriate in terms of risks and mitigations, and access and affordability considerations. This general type of CMC technology has been proven to be scalable for products which meet proof of concept, as evidenced by the COVID vaccine efforts earlier in this decade. Budget and timelines are reasonable. CMC development and regulatory proposals are reasonable.

- The planned preclinical studies include addressing current gaps in testing to meet the requirements for readiness of a pre-IND package and IND. Currently, the nonclinical studies are compelling enough to progress to pre-IND and meeting with FDA.

- From a regulatory standpoint, the authors have not yet participated in a pre-IND but have submitted another drug RNA candidate which received pre-IND feedback--so there is a familiarity with FDA expectations for this drug candidate.

  As part of the funding package, a nonclinical regulatory expert in oligonucleotides (ex-FDA) will oversee the pre-IND and IND studies and act as adviser to the team.

- The team is aware that GMP-grade material is required for the two species of toxicity studies and they have planned and budgeted for this accordingly, although manufacturing costs appear minimal.

- The stages of development appear to be well-planned and appropriately costed for nonclinical development and feasible within the 5-year timeline.

Project Team and Resources

- They have experience of developing another product with pre-IND meeting for it, so the pre-IND process is understood.

- The team appress to have in depth experience in this space, i.e. taking preclinical innovation and proof-of-concept through the clinical trials.

- Strong project team.

- CMC efforts seem reasonable and appropriate. Engagement of FDA in earlier efforts shows willingness to work with the regulatory agency and seek their advice.

- The planned team appears appropriate and employs appropriate-level staff and expertise at each stage of the project from scientific, regulatory and junior staff-senior leadership to meet the objectives. The functional expertise appears to be in place including selection of laboratory scientists to complete in-house nonclinical work; selection of a nonclinical GLP lab for animals studies; selection of a GMP manufacturing facility; regulatory consultant; regulatory submission team to meet the pre-IND and IND expectations and clinical consultant with experience of RNA oligonucleotides to assist with clinical protocol planning.

Population Impact

- ACM treatments that are more effective will have impact across Californians, sexes, races and across the globe. The product has a high chance of being safe. The clinical study is in health volunteers to start, and this seems entirely appropriate and will then inform the studies in ACM patients. Key to that would be the choice of ACM patients and why. Presumably based on the ability to see the action needed (ie. the impact of efferocytosis) and the capability to prevent (and reverse) disease.
- The applicant appears cognizant of the intended clinical population and that feasibility of testing will be enabled by genetic testing of ACM patients. Some caveats appear in demographic groups who may not know they have the disease until a cardiac event occurs, urging the need for genetic testing of at-risk groups.
- Proposed approach seems adequate.
- Affordability and accessibility are not addressed well.
- Affordability and accessibility hadn't been described although the project is very early.

Application #	PDEV-19156
Title (as written by the applicant)	Gene Therapy for Alpha-1 Anti-Trypsin Deficiency
Therapeutic Candidate (as written by the applicant)	Our candidate encodes the A1AT protein (Serpina 1) driven by a ubiquitous promoter and encapsulated an evolved lung tropic AAV capsid developed 4DMT
Indication (as written by the applicant)	Alpha-1-Anti Trypsin Deficiency Lung Disease
Unmet Medical Need (as written by the applicant)	Alpha-1 Antitrypsin Deficiency (A1ATD) is a rare genetic lung disease where low A1AT levels cause lung damage and emphysema. Current treatments are limited, but gene therapy offers hope to restore A1AT, improving health and survival.
Major Proposed Activities (as written by the applicant)	• Completion of IND Enabling Nonclinical Studies • GMP Manufacture to support IND Filing • Clinical Protocol Development for IND filing
Statement of Benefit to California (as written by the applicant)	The candidate's differentiated efficacy and convenient dosing profile, compared to the standard of care, is expected to deliver meaningful benefits by significantly improving quality of life for people with severe A1ATD while also reducing healthcare costs and burden through fewer hospitalizations, emergency visits, and long-term disease management needs.
Funds Requested	$5,916,702
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	85
Median	85
Standard Deviation	1
Highest	87
Lowest	85
Count	12
(85-100): Exceptional merit and warrants funding, if funds are available	12
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel’s discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in

the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

Key Strengths and Weaknesses

- In terms of value proposition, several other first-in-class molecules are in development for the treatment of alpha-1 antitrypsin deficiency (A1ATD) that could impact positioning this candidate in the marketplace. The applicant argues that this project has a high probability for regulatory success and commercialization because 1) it utilizes an AAV vector platform clinically validated for lung-targeted gene therapy, 2) existing safety and biodistribution data will be leveraged for IND submission leaving a clear path to FIH clinical studies, and 3) lung-targeted gene therapy using the applicants vector delivery platform will express therapeutic A1AT at the desired site of action over long periods of time, without peak-to-trough exposure difference, and be potentially re-dosable, increasing the effectiveness and durability of this treatment over current available treatments with sustained expression potentially up to three years.

- However, patients with pre-existing lung disease may exhibit greater sensitivity to immune responses or local inflammation. Serial lung function monitoring (e.g., spirometry, imaging) will be incorporated to detect early changes. As A1ATD-related lung disease rarely presents in children, initial studies will focus on adults only, thus limiting the therapeutic potential. Because AAV is generally non-integrating, persistence of therapeutic expression may decline over time. Clinical durability will be evaluated using lung function measures, biomarker analysis (e.g., A1AT protein levels), and bronchoscopy. As with all gene therapies, delayed or unforeseen adverse events may emerge. Long-term patient follow-up in accordance with FDA guidance would be required.

Value Proposition

- This AAV candidate therapy represents a compelling, stage-appropriate, and mechanistically grounded improvement over existing therapies. Its potential to meaningfully reduce disease progression, treatment burden, and healthcare costs is high. Remaining uncertainties include validation of clinical durability and affordability at commercial scale, but the integrated manufacturing and platform safety data substantially de-risk translation.

- The applicant's efforts are aimed at completing preclinical development of gene therapy for A1ATD which causes irreversible emphysema and end-stage lung disease. Their product should produce better quality of life and overall survival.

- The impact for those affected by this disease is quite significant if plans develop as expected; current treatments are not particularly effective.

- Applicants report that because of the limited success and high treatment burden of the standard of care augmentation therapy, it is only recommended for less that 30% of the current treatment population. There are also payment and insurance obstacles often in the way. Their plans would be to supplant this system.

- The applicant provides a detailed and convincing analysis of the superiority of their product over the other products in the five potential future therapeutic classes for treatment of this disease, including the novel augmentation therapies.

- Applicant surveys of physicians and providers give them support for the practicality of the treatment's uptake by providers and patients.

- The field of replacement therapy for patients with A1ATD is very active, with approved augmentation treatments showing moderate results and two ongoing gene therapies in development using AAV vectors.

- Current standard of care includes several types of approved augmentation therapy, but overall these treatments lack efficacy, have a tedious administration schedule, and put a large burden on the healthcare system. Accordingly, the candidate can address all of the issues with current treatment options, and the applicant has the opportunity to penetrate a high-need market.

- Several other first-in-class molecules are in development for the treatment of A1ATD that could impact positioning of this candidate in the marketplace. However, the applicant argues that this project has a high

probability for regulatory success and commercialization because 1) it utilizes the clinically validated AAV platform for lung-targeted gene therapy, 2) existing safety and biodistribution data will be leveraged for IND submission leaving a clear path to FIH clinical studies, and 3) lung-targeted gene therapy using the AAV delivery platform will express therapeutic A1AT at the desired site of action over long periods of time, without peak-to-trough exposure difference, and with potential for re dosing, increasing the effectiveness and durability of this treatment over current available treatments with sustained expression potentially up to three years.

Rationale

- Strengths include human clinical capsid data, extensive GLP aerosol experience with the vector in a relevant preclinical model showing lung transduction and tolerability, and in-vitro functional A1AT activity. Gaps remain around (i) absence of a formal GLP tox study specific to the candidate (although FDA accepted platform reliance from another candidate using the same vector), (ii) limited systemic biodistribution signals in liver/heart (very low level) that warrant monitoring, and (iii) re-dosing feasibility still under evaluation. These are reasonable for the stage, but they define near-term de-risking priorities.
- The capsid technology used to develop the candidate has been used in clinical development and has a safety profile established in patients. As of July 1st, 2025, more than a dozen patients have been treated with investigational product using this capsid with follow-up ranging from approximately two to over 36 months and administration has been generally safe and well tolerated.
- The investigators have developed a delivery vector, AAV capsid which is more effective at delivering into the lung and achieves high expression of the delivered gene. However, it is difficult to assess the difference in efficiency because there is no data comparing the new vector developed by the applicant and those being evaluated in ongoing clinical trials.
- Multiple supporting studies were presented. Extensive GLP studies in over 40 large animals have demonstrated robust transduction and lung biodistribution, transgene expression, and safety following aerosol administration with this AAV vector based investigational products.
- In vitro, the candidate drives dose-dependent A1AT expression and neutrophil-elastase inhibition (functional activity). Clinically, the shared capsid in a different pulmonary indication shows 89–100% airway cell transduction with expression maintained ≥ three years, indicating durable human lung transduction.
- Relevant preclinical model studies with the vector demonstrate robust lung biodistribution and a high no adverse event level. Taken together, these data support potential disease modification if pulmonary A1AT levels reach therapeutic thresholds.
- The discussion of the scientific reasoning behind the particular approach and route of administration as compared with potential competitors was quite robust.
- Their previous work gave this group rather strong evidence of the efficacy of the approach they planned to use.
- Based on feedback from FDA, a nonclinical repeat dose toxicology study would be required to mimic the intended clinical dose and dosing regimen for the candidate therapy for A1ATD. This study is planned.
- The only limitations noted in the data presented were that supportive data from their market consultants conducting the applicants initial access and affordability research, such as landscape analysis and market access research, appeared more anecdotal than scientific, and that the only two letters of support were from their two subcontractors.

Project Plan and Design

- Collectively, the proposed PDEV activities are necessary, well-sequenced, and appropriately scoped to achieve IND readiness. The budget appears justified by prior platform efficiencies, and risk controls and early access considerations enhance translational credibility. The main vulnerabilities are analytical validation timing and re-dosing immunogenicity assumptions, which warrant close tracking in the execution phase.

- The applicants appear to be rather in the beginning stages of doing the work required for the IND clearance, but they have prior success negotiating this landscape. They have met with the FDA for an IND enabling strategy plan development.
- The data provided regarding market uptake and affordability seems anecdotal but convincing.
- The preclinical studies are in advanced stages, with in vitro and in vivo studies already completed, including those in large animal models for this candidate. The applicant has developed another candidate using the same vector which is already in phase 1/2 clinical trials. According to communication with the FDA, part of the preclinical studies for the vector currently in clinical trials can be applied to the candidate being developed for A1ATD.
- Based on regulatory feedback, the nonclinical, CMC and clinical plan seem reasonable and manageable within the 30-month timeframe allocated in this late-stage development program.
- The main caveats to the program relate to patient population (adults only); potential for diminishing signal; known off-target effects of AAVs. Immunogenicity is also a significant concern.

Project Team and Resources

- The leadership, staffing, and infrastructure are well matched to IND-stage complexity. The proposal demonstrates strong institutional memory from prior AAV submissions, mature internal CMC systems, and clear coordination mechanisms. Remaining execution risk is moderate and confined mainly to immunogenicity assay validation, not organizational capacity.
- The PI and their team seem very qualified and motivated.
- A complex plan for coordination and execution has been outlined base in part one success in developing similar products and bringing them to market.
- The applicant team have outlined the costs contractors and resources that they would require to bring the project to successful completion.
- The group have had success in the past; this is the business for which they exist.
- The team have extensive experience in gene therapy and are well qualified to carry out the proposed experiments.
- Eight different applicant organization staff are allocated to the project with different degrees of involvement. The allocation of staff and resources to reach an IND seems robust.

Population Impact

- The outreach plan commits to demographically representative enrollment and engaging communities that “don’t traditionally participate” in trials which supports downstream adoption and safety generalizability. Concretizing tactics (e.g., travel stipends, childcare, language access) in the operations plan would make the equity intent more actionable.
- The data and the approach they presented demonstrate the applicants have a good understanding of the disease, the environmental complications (like smoking) that would affect the success of the treatment and its uptake.
- They provided good data on the demographics of this illness and the current state of the art in treatment.
- Yes, they have interviewed and utilized various patient support groups and have drawn support for their proposed approach.
- Inhaled AAV therapy for A1ATD presents theoretical risks primarily related to immunity, off-target distribution,

lung delivery, and long-term safety. These risks are expected to be manageable based on prior experience and will be addressed through prophylactic immunosuppression, controlled pulmonary dosing, serial functional monitoring, shedding studies, and long-term follow-up.

Application #	PDEV-19152
Title (as written by the applicant)	Advancement of a myotropic, liver-detargeting therapy for LGMD2i/R9
Therapeutic Candidate (as written by the applicant)	[redacted candidate name] - A next-generation AAV gene replacement of FKRP
Indication (as written by the applicant)	Limb girdle muscular dystrophy 2i/R9 (not represented in CIRM portfolio)
Unmet Medical Need (as written by the applicant)	LGMD2i/R9 is a muscle wasting disease caused by a mutation in the FKRP gene. Our approach replaces the mutated FKRP gene with a healthy copy and is delivered by a next-generation AAV capsid that avoids the liver (safety issue) and has strong muscle tropism.
Major Proposed Activities (as written by the applicant)	• Chemistry, manufacturing and control scale-up; assay development and drug production • GLP toxicology study and pharmacology study of combination of candidate/Ribitol • IND preparation and submission; Clinical site initiation
Statement of Benefit to California (as written by the applicant)	As one of the largest and most diverse states in the US, California has a significant population of LGMD2i/R9 patients. [redacted candidate name] is a one-time infusion that is cost effectively priced and will reduce healthcare spend for the state, reduce patient and caregiver burden and most importantly, improve the quality of life of patients impacted by the disease. Moreover, the use of AAVMYO2 capsid as a platform will facilitate quicker development of future therapeutics for different diseases.
Funds Requested	$7,350,596
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	85
Median	85
Standard Deviation	2
Highest	87
Lowest	80
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	10
(1-84): Not recommended for funding	3

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

Key Strengths and Weaknesses

- Strengths: (a) Superior muscle tropism of proposed vector. (b) Potential of lowering viral dose in combination therapy (c) Aligned with pre-IND meeting (d) Team members and partners.
- Weaknesses: (a) Uncertain landscape based on timing and decision to approve ribitol.
- The value proposition was originally the use of a muscle targeting vector that may allow for a lower effective systemic dose which would improve safety and potential cost savings.
- The necessary pivot to a combination regimen approach based on approval of another drug during clinical development affords additional potential to further reduce vector dose.
- Valuable delivery vector applied to an important target.
- Key strength is the novel capsid used and its potential to lower dose and toxicity; primary weakness is the competition that exists and overall concerns with a systemic, muscle-targeted AAV (regarding durability), however the differentiated approach warrants exploration.

Value Proposition

- There is currently no FDA approved therapy.
- The proposed therapeutic candidate utilizes a capsid that possesses muscle tropism combined with low tropism for liver (and low cardiac expression to reduce potential cardiac toxicity). This makes it potentially superior to two other gene therapy protocols (Phase I/II) currently in trial that are conventional AAV9 based (with considerable liver tropism).
- BridgeBio's small molecule, ribitol, is in Phase III and works upstream of FKRP (Fukutin-Related Protein) to improve glycosylation of alpha-dystroglycan. While BridgeBio/ribitol's primary endpoint is at 36 months – they have announced that they will file for accelerated approval based on increased glycosylation as a surrogate endpoint (complete enrollment of FORTIFY in Sept 2024; has received rare pediatric disease designation, fast track designation, and orphan drug designation for LGMD2I/R9 from FDA). This proposal assumes, given the unmet medical need, that ribitol is likely to be approved – so the proposed plan is to be prepared to test the applicants' candidate in people who would already be on it – which may also allow lowering the dose compared to its use as a monotherapy.
- The treatment landscape for LGMD R9 (Limb-Girdle Muscular Dystrophy R9) has recently changed - due to the anticipated approval of a new standard of care, dietary supplementation with ribotol, the program has pivoted from an initially proposed monotherapy to a combination regimen therapy.
- The developers have pledged to price the drug at "cost+10%" / ~$750K, which would make it considerably more affordable than other gene therapy products.
- The value proposition is the use of a muscle targeting vector that may allow for a lower effective systemic dose which would improve safety and potential cost savings.
- Following dose optimization the anticipated synergistic effect could result in lower doses of vector necessary for the additional clinic benefit of the combined modalities.

- Borderline value proposition especially if safety becomes a concern.
- Sound scientific approach however general concerns about systemic AAV delivery; differentiator in using novel AAV targeting muscle in a competitive space. Clear unmet medical need; likely to be expensive treatment; question about need for redosing given this targets many cells and muscle. No issues with patient or caregiver uptake; continued concern with healthcare reimbursement.

Rationale

- LGMD 2I/R9 is an autosomal recessive disease, caused by missense variants in the FKRP gene. Fukutin-related protein is required for glycosylation of alpha-Dystroglycan, and these missense mutations result in its hypoglycosylation, disrupting interaction of muscle cells with laminin in the ECM, driving contraction-associated muscle injury. This LOF makes LGMD R9 a rational candidate for gene therapy to replenish functional FKRP.
- FKRP is an enzyme and not a structural muscle protein – making it an attractive candidate for replenishment via gene therapy.
- Good scientific rationale using a muscle targeting capsid.
- Applicants' plan to complete non-clinical and CMC activities to support the submission of an IND as a monotherapy (based on completed pre-IND). Additionally, they argue that since patients will gain access to ribitol - they plan to perform non-clinical pharmacology to investigate the dose response relationship when [redacted candidate name] is used in combination.
- Choice of promoter (tMCK versus CK8e; the latter, used in their prior study led to cardiac toxicity and murine death in 10 days) to have lower cardiac expression (100x less cardiac expression).
- Choice of capsid is preferentially myotropic and has low liver tropism (NHP and mouse). This capsid was selected upon screening 25 different capsids (including AAV9 and AAVrh74) in large animal models (Charles River and Grim lab). This also showed negligible liver dosing in the FKRP mouse model (orders of magnitude difference with AAVrh74).
- Work up for pre-IND meeting completed: capsid and promoter selection; dose response pharmacology study demonstrating improvement in muscle structure in the FKRP model (reduced central nuclei; improvement in fiber size distribution; cardiac function was only marginally better at high dose); extended study (12 m) demonstrating long-term persistence of candidate and improvement in muscle function, and no evidence of cardiac tox.
- At FDA pre-IND meeting, the IND enabling studies (Aim 2) and manufacturing requirements (Aim 1 and Aim 4) to support an IND were agreed upon.
- The rationale for gene replacement as a therapeutic approach for this disease is sound.
- The preclinical data are supportive but limited.
- Safety issues need to be carefully considered.

Project Plan and Design

- This late PDEV project is guided by the pre-IND meeting.
- Choice of activities and partners are appropriate.
- It is a bit unpredictable how the anticipated approval of ribitol will determine the timing and tone of the IND submission – although the forward-looking planning is commendable.

- This is a late PDEV proposal with 5 Aims over 36 months, for which CIRM funding is requested.
- The plan is designed that addresses comments received after a successful preIND meeting.
- While assessing toxicity in animal model only has been accepted by FDA it is not clear that the current design will be sufficiently robust/technically feasible to assess proposed biomarkers at the interim timepoints. Further justification of interim timepoints is needed.
- To better understand relevant safety margins in the GLP toxicity study it seems more appropriate to optimize doses in the pharmacology study to demonstrate both an additive benefit and safety margin in animal model of disease. The goal in both studies would be to confirm that lower systemic doses of vector can be given that demonstrate effective and maximally effective doses.
- CMC costs are understated.
- Unclear what work was previously done; this reviewer believes the CMC development costs are understated given it is a novel capsid, especially analytical; stability only out to 12 months (typically should go to 24-36 months).

Project Team and Resources

- Applicant has a track record of moving various drugs for neuromuscular disease along the drug development pathway. They have the necessary expertise for project management, CMC, regulatory affairs, IND writing, etc.
- Lead PI is an exemplary clinical lead.
- [Name Redacted] is an appropriate lead for pharmacology and GLP tox studies – the bulk of this project.
- Reimbursement and accessibility will be led by an industry veteran.
- Use of standard CDMOs and cGMP manufacturing sites: one to support AAV Therapeutic development, one for specialty pharmaceutical manufacturing, and one for pharmacology and tox studies.
- Both CDMO and CRO have been identified to support IND enabling activities.
- Strong team with record in rare disease.
- Good team with research depth, consultants are sound, and service providers are good. One academic institution for manufacturing may raise concerns with depth and expertise in development and manufacturing.

Population Impact

- Appropriate consideration of the need to consider ribitol's potential entry into the treatment space.
- Broad population susceptibility, with different missense variants, although all should still benefit from replacement with wild-type FKRP. People of European ancestry, LGMD R9 is one of the most prevalent LGMDs and the causative missense variants are relatively uniform and well characterized. LGMD R9 is also known to impact South American, Asian and Indian populations, although their missense variants have not been fully characterized.
- There is a good understanding and communication patient population through the applicant organization.
- More discussion is needed for different missense variants
- Target appears to have competition in the gene therapy space; need information about capsid to understand if approach will promote success over competition No concerns with adoption or use but seems it will be a

race to who gets approved first.

Application #	PDEV-19149
Title (as written by the applicant)	Microglia replacement therapy for CSF1R-related Leukoencephalopathy
Therapeutic Candidate (as written by the applicant)	The therapeutic candidate is an allogeneic, stem-cell–derived microglial replacement therapy made from a clinically compatible GMP-grade iPSC line.
Indication (as written by the applicant)	ALSP (Adult-onset Leukoencephalopathy with Axonal Spheroids and Pigmented Glia) is a rare, progressive neurodegenerative disorder.
Unmet Medical Need (as written by the applicant)	ALSP is a fatal brain disease with no approved treatments. Current care is limited to symptom management. The therapeutic candidate aims to slow or halt disease progression with a one-time therapy, addressing a critical gap for thousands of patients worldwide.
Major Proposed Activities (as written by the applicant)	• Finalize the manufacturing process for the proposed cell therapy. • Complete safety and toxicology studies that support the use of the proposed cell therapy in humans. • Finalize all aspects of the clinical plan and submit IND to FDA, allowing the start of clinical trials.
Statement of Benefit to California (as written by the applicant)	The proposed research addresses a fatal neurodegenerative disease with no approved treatments. By advancing a one-time, potentially curative cell therapy, this project offers new hope to affected Californians. It supports jobs, innovation, and clinical infrastructure in California, and could reduce long-term healthcare costs by delaying or preventing institutional care. Success may also establish California as a leader in microglial cell therapies.
Funds Requested	$12,993,456
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	84
Median	85
Standard Deviation	4
Highest	90
Lowest	75
Count	12
(85-100): Exceptional merit and warrants funding, if funds are available	6
(1-84): Not recommended for funding	6

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

Key Strengths and Weaknesses

- Applicants haven't tested how residual, diseased microglia will interact with the therapeutic transplanted microglia; this needs to be tested before clinical trial.
- A possible solution to a strong clinical need. Positive trial results would be highly impactful for patients. Results from a bone marrow transplant (BMT) study conducted in China seem important to define the plans for this product to be delivered by direct brain injection, when bone marrow transplant might work.
- Strong preliminary data demonstrating mechanism of action for a fatal genetic disease.
- Well-designed manufacturing strategy and project plan with strong risk mitigation strategy. Scale-up studies demonstrating production of material at appropriate scale would strengthen the application.
- Strengths: Strong value proposition for patients, chemistry, manufacturing and controls (CMC) is well planned out from tech transfer onward, using an established delivery device.
- Weaknesses: FDA feedback on the mouse model and the need to include diseased microglia to understand the interaction between diseased patient cells and applicant's transplanted microglial cells. This work has not yet been completed and presents risk to the program if results are unexpected. In addition, BMT has shown promise as an alternative therapy with low number of participants, but it requires ablation. That isn't ideal for the patient. Therefore, this grant remains fundable based on the potential advantages of delivery without ablation and as an alternative to BMT.
- Large unmet clinical need with no alternative therapies to treat underlying cause of disease. The resulting pathology includes cognitive and motor decline, neuropsychiatric symptoms, and ultimately death within approximately six years of symptom onset.
- The nonclinical development studies indicate that the candidate could be a compelling therapeutic resulting in disease modifying activity in clinically relevant animals models of disease.
- Collectively, the plan is well-considered and achievable with the proposed budget and allocated timeframe factoring in time to address any CMC setbacks and time to order preclinical model delays.
- All team members required to get to an IND have considerable experience in the required areas including CMC, nonclinical, regulatory planning, writing and submissions, and clinical planning.
- Collectively, the population impact has been well-considered. Applicants highly cognizant of community outreach; communication vehicles and liaising with the ASLP community.
- The product is an allogeneic, stem-cell–derived microglial replacement therapy made from a clinically compatible GMP-grade iPSC line. This would be the first of its kind.
- Target population are patients with ALSP (Adult-onset Leukoencephalopathy with Axonal Spheroids and Pigmented Glia), a rare, progressive neurodegenerative disorder. Patients have a mutation in CSF1R gene, which encodes a receptor tyrosine kinase that is expressed on the microglia cell surface and is necessary for microglia development, survival, and maintenance.
- While there is no cure, and a recent trial failed, BMT in eight patients halted disease progression. However, this is a high risk intervention due to the required myeloid ablation conditioning. The applicant's product

would bypass such an intervention thereby significantly de-risking the therapeutic approach.

- Strong scientific merit and commitment from the combined applicant team.
- The pre-IND meeting response expresses concern about the possible interaction of patient microglia cells and the graft cells. The applicant will generate these data via another source of funding, but the timeline for this is not clear. What is the contingency plan if these experiments do not show the expected results?
- Strong team, but the safety issues need to be addressed.
- The pre-IND meeting response has questions regarding the value of the a mouse model that does not develop motor defects and limits efficiency studies to no behavioral endpoints. This could be problematic in the future.

Value Proposition

- The goal is to provide long-lasting benefit from a single dose, as opposed to current standard of care (SOC) which is limited to symptom management.
- Addresses a fatal genetic mutation leading to ALSP by replacing defective microglia to effectively cure disease. Current SOC is chronic symptomatic management of associated neurological complications and hospice/palliative care.
- Comparative analysis based on cost of goods (COGS) suggests significant cost savings versus SOC. Scalable platform has the potential to lower costs further.
- Humanized mouse models demonstrate robust therapeutic benefit.
- Delivery is compatible with existing surgical workflows.
- Strong value proposition if the candidate is successful.
- Value proposition is strong. There is the potential alternative of BMT, but this is still early data from small participant numbers and requires ablation. This therapy may be an attractive alternative for some patients even if BMT is an option.
- There is a significant value proposition offered by this cell therapy to reverse course of a progressive, deadly disease for which there are no available treatments. The value proposition is likely to significantly reduce burden of costs on patients, families and healthcare systems alike.
- The applicant's approach does not require myeloablation.
- Broader application in regenerative neurology is limited to diseases with a microglia depleted niche.
- The interest of patients currently under consideration for the applicants future clinical trial in the alternative BMT approach is not clear.
- Patients that cannot tolerate BMT and have no other treatment options are not considered to be the most urgently-to-be recruited patients that could uniquely benefit for the proposed approach.

Rationale

- The rationale for this project is strong. One gap highlighted in the discussion is how to assess the interaction between diseased mutant and the transplanted microglial cells preclinically. This work has not yet been completed and presents risk to the program if the residual mutant cells negatively impact the transplanted microglia.

- Demonstrated mechanistic link between CSF1R loss and microglial depletion.
- Relevant murine model exists and has been used extensively to demonstrate mechanism of action in vivo. Data recapitulated using multiple iPSC lines.
- The microglial cell candidate is proven highly safe in murine model with over 1,500 grafts without detected tumorigenicity and low immunogenicity in long-term.
- Good regulatory strategy.
- No idea how residual host microglia will interact with the drug product.
- Preliminary data show robust engraftment and reversal of pathology in a murine model which has an empty niche. Transplantation in a fully occupied niche in healthy animals also shows engraftment (although the relevant figure is not clear; it lacks human nuclear labeling. This suggests there may be no presence of human cells and is confusing.
- It's mentioned that this is the first therapy of its kind, but little other details, including the population impacted, are provided.
- Collectively, the nonclinical data indicate that the candidate could be a compelling therapeutic resulting in disease modifying activity in clinically relevant animals models of disease.
- Proliferation potential of the candidate is not described. How long will graft survival and regeneration last? Note that microglia have a turnover rate of four weeks in humans.
- The rationale for patient selection is unclear. Could patients with advanced microglia loss represent better responders to the therapy than patients with minimal loss? What data underlie the assumption that disease stage/progression is a directly result of the percentage of microglial death?

Project Plan and Design

- Overall the nonclinical testing strategy appears robust. Collectively the plan is well-considered and achievable with the proposed budget and allocated timeframe, factoring in time to address any CMC setbacks and time to model procurement delays. The studies factor in testing of the delivery device that will be used clinically to assess any potential issues in a large animal model.
- That the commercial GMP iPSC bank is obtained from reputable vendor and expanded into large MCB for all developmental work by same vendor is a strength. This reduces time risk associated with tech transfer of starting material.
- CMC studies are adequate and include all tests that were requested in the pre-meeting documents.
- Technology will be transferred to a university biomanufacturing center. It's a qualified CDMO with expertise in process development, cGMP readiness and iPSC-derived therapeutic manufacturing.
- The university manufacturing center will provide confirmation that the candidate drug product maintains viability, identity, purity, and potency after administration through the FDA-approved cannula delivery device, generating administration feasibility data to support the IND and demonstrate deliverability to patients.
- Detailed and reasonable manufacturing process flow. CMC plan is straightforward and contains appropriate milestones.
- Defined risk mitigations are appropriate and include iPSC backup, alternative CDMO, manufacturing contingencies, comparability, and negative safety. Contingency costs will be incurred by the applicant.
- Mouse model experiments are risky.

- Project plan from tech transfer onward is well mapped out. It would be beneficial to describe the process development activities in more detail.
- Uncertain whether the scale-up has been completed.
- It's unclear to what extent scale-up has already been completed.
- iPSCs are expanded as aggregates in spinner flasks with stirred tank reactors for scale-up. It's not clear if this process has already been completed.
- Timeline appears appropriate for tech transfer and manufacturing at CDMO. Relative lack of details on expansion, differentiation, and scale-up suggests the potential for extensive process optimization that may expose timeline risk.
- Large animal studies are proposed for scaling and safety, but analysis of graft longevity (i.e proliferation potential of graft cells) is not included.
- Affordability is not clear compared to BMT.

Project Team and Resources

- Strong leadership of PI and team.
- Strong manufacturing partners with institutional support.
- Team and resources are appropriate.
- All team members required to get to an IND have considerable experience in the required areas including CMC, nonclinical, regulatory planning, writing and submissions, and clinical planning.
- The team is excellent.
- Recruitment of four consulting companies for IND preparation seems excessive.

Population Impact

- Applicants built deep engagement with the Sisters Hope Foundation and United Leukodystrophy Foundation, resulting in direct relationships with patients, caregivers, and a broad network of KOLs and treating clinicians.
- The team has close interaction with patient cohorts. The clinical co-leader has over 50 confirmed patients actively in their care, with approximately one new patient per week, ensuring a sufficiently large pool of patients for recruitment to the proposed trial.
- Collectively, the population impact has been well-considered. Applicants highly cognizant of community outreach; communication vehicles and liaising with the ASLP community.
- Highly motivated community to participate in a new therapeutic clinical trial.
- The proposal didn't include population impact and the number of affected people in the state.
- No mention of population impact.
- The project takes into consideration the potential impact of the proposed microglial cell therapy across affected patient populations. In addition to treating patients with the most aggressive mutations leading to rapid neurodegeneration and midlife mortality, these microglial cells may also benefit those with weaker penetrance or less pathogenic CSF1R variants by delaying or preventing late-stage neurodegeneration.

- Although the candidate requires MRI-guided stereotactic intracerebral injection, this is already a routine practice at major academic and regional medical centers worldwide, supported by established neurosurgical infrastructure. Adoption will therefore leverage existing networks rather than requiring new systems.

- To further broaden access, the applicant is implementing a hub-and-spoke model in which procedures are centralized at specialized centers while follow-up care occurs locally, reducing burden on patients and families.

- By integrating specialized delivery centers with proactive efforts to streamline diagnosis, the applicant is well positioned to provide equitable and timely access to the candidate across diverse geographies.

Application #	PDEV-19131
Title (as written by the applicant)	Autologous iPSC-derived progenitor smooth muscle cells for treatment of urinary incontinence
Therapeutic Candidate (as written by the applicant)	Autologous iPSC-derived progenitor smooth muscle cells (pSMCs). Patient fibroblasts are reprogrammed into iPSCs and then differentiated into pSMCs.
Indication (as written by the applicant)	Moderate to severe stress urinary incontinence (SUI) that requires daily pad use. SUI is the involuntary leakage of urine with physical activities.
Unmet Medical Need (as written by the applicant)	SUI is common. While the surgical sling is effective, it fails in 33% of patients. Recurrence after surgery often requires more surgery which has even higher failure rates, leaving these patients with limited treatment options. There is an unmet need for non-surgical options for these patients.
Major Proposed Activities (as written by the applicant)	• Completion of IND-enabling activities, including GMP cell manufacturing and definitive preclinical animal studies • Clinical protocol development • Preparation and submission of an IND
Statement of Benefit to California (as written by the applicant)	Urinary incontinence (UI) is common. Approximately 1 of every 2 non-institutionalized women older than 65 develops some type of UI. UI is associated with depression, poor quality of life, increased risk of falls, hospitalizations, and nursing home placement. Surgery is effective for SUI but 33% will develop recurrence. Californians would benefit from the candidate therapy as it is a non-surgical therapy for those who have failed surgical therapy or for those who are not able to undergo surgery.
Funds Requested	$7,499,999
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: 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	83
Median	85
Standard Deviation	2
Highest	85
Lowest	80
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	8
(1-84): Not recommended for funding	6

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

Key Strengths and Weaknesses

- Strengths: Clear unmet medical need and large patient population. Nonsurgical method is advantageous, especially for older patients. Delivery method exists (currently used for bulking agents). Preclinical model is appropriate and the product shows efficacy.
- There is certainly a large unmet medical need for the development of treatments which impact SUI a condition which disproportionately impacts older post-menopausal women.
- Strengths of the application relate to the large unmet clinical need and provides a good alternative to surgery. Potential for significant patient enrollment and engagement based on proposed plans.
- The applicants have developed a rat model of SUI which is a strength of the application. They have also developed a directed differentiation process to manufacture Progenitor Smooth Muscle Cells which show an impact in the animal model - both strengths.
- Scientifically rational proposal to address an extremely important clinical need. Better justification of doses and dose extrapolation is needed.
- The are issues around manufacture (purity of the cells, cryopreservation etc) that need to be addressed before this can be funded. The area is important and would have important impact.
- Weaknesses would include the lack of concurrence between the applicants and FDA as it relates to CMC. Also the total process is quite long - to make iPSCs, differentiate them into PSMCs and expand them is a ~40 day process - given this is an autologous product I think there are significant challenges in making the product in a cost effective manner.
- CMC and nonclinical data needs further work before further translational work.
- The applicants need to consult a CMC specialist to advise them on their development plans.
- Weaknesses: Autologous therapy means high cost, unsure of cost/benefit. The proposal mentions that the risk associated with iPSC-derived cells is unknown and doesn't discuss how they plan to ensure product purity (no residual iPSCs or off-target cells). Lots of work to do on CMC, based on Pre-IND feedback from FDA.
- It was noted that FDA provided extensive feedback on the CMC plans including critical milestones and it is unclear whether there is acknowledgement of the manufacturing deficiencies and the cost on timelines associated with meeting them. From a nonclinical perspective there were concerns relating to the translation of cell number from mice to rats and oversight of the nonclinical testing plan is required.
- I would expect the pSMCs to be rejected in the animal model so I am puzzled that they are not.
- I think there is a significant risk that the project will not be achieved in a timely manner and on budget.
- Weaknesses:
    - Reprogramming method: Insufficient independent data support the long-term stability and differentiation capacity of uBriGene-derived iPSCs. The proposal presents iPSC reprogramming data and three different protocols but plans to use a different system for translational work: the

uBriGene RNA-LNP reprogramming kit, optimized for PBMCs. The company claims high efficiency, safety, and suitability for autologous therapies, with reduced immune rejection risk. A Drug Master File has been submitted, and GMP-compliant clinical iPSC banks reportedly exist. However, there is no independent, peer-reviewed validation of uBriGene's long-term genomic stability, differentiation potential, immunogenicity, or performance compared with established reprogramming methods (e.g., Sendai virus, episomal vectors). This raises concerns regarding reproducibility and safety.

- ECM analysis: Only elastin was examined; other ECM components (collagen) should also be evaluated.
- Mechanisms of repair: No evidence is presented to confirm persistence, engraftment, or integration of injected human cells (e.g., via human-specific immunostaining of mitochondrial or nuclear proteins).
- Animal model limitations: rationale for dose justification is not found - similar doses are proposed for two different size species - mice and rats. The use of NGS mice for peri-urethral injections of 4–10 million SMCs is problematic given anatomical constraints and risk of off-target delivery, even if FDA-recommended.
- Functional assays: Gel contraction or similar assays should confirm that pSMCs differentiated from uBriGene kit-produced iPSCs differentiate into mature, functional SMCs.
- Cell purity is a big concern: The team removed a FACS step to improve yield, speed up the process of obtaining the required number of cells, but purity of the injected cell population is uncertain. Validation with both progenitor (e.g., SPP1, MYH10, ICAD) and mature SMC markers (SMA, SM22, CNN1) is necessary.
- Transcriptomic analysis: Single-cell transcriptomic comparisons of pSMCs were made only against embryonic stem cells. Proper benchmarking requires comparison with primary human bladder SMCs.
- Engraftment vs. proliferation: Claims of in vivo stabilization of pSMSs are based only on in vitro passaging, which does not recapitulate in vivo engraftment dynamics
- Details regarding the use of cryopreserved cells are unclear.

Value Proposition

- Urinary incontinence has a high rate of prevalence in older women, and significantly impacts quality of life. Current treatment options include injection of bulking agents which don't provide a durable solution and sling surgery, which has high failure rates. Recurrence after surgery often requires repeat surgery with even lower cure rates. There is also a population of elderly women that cannot tolerate a surgical procedure. For all of these reasons, a non-surgical, curative approach is desired with iPSC-derived smooth muscle injection as a potential solution.
- SUI disproportionately affects older women. Current treatments include physical therapy, injection of bulking agents or sling surgery involving synthetic mesh or autologous fascia. While these approaches often lead to improvements in SUI those improvements are mostly temporary and repeat treatment is less efficacious.
- Many affected individuals choose to use incontinence diapers but over time these can lead to skin irritations and infections. In addition this is a recurring cost and over time the costs mount up.
- Large unmet need.
- Given that there is a large unmet medical need, with current treatment options lacking efficacy and/or durability, there would be demand for such a therapy. With demonstrated clinical proof of concept, additional focus on reducing cost and increasing accessibility would be warranted and could be achievable.

- Current SUI treatments for older women are limited: bulking injections require repetition, and sling surgery carries risks like erosion and chronic pain. The proposed iPSC-derived cell therapy could replace current treatments for postmenopausal women with stress urinary incontinence (SUI), such as bulking agent injections and sling surgeries. It may especially benefit women unable to undergo or who failed surgery. SMC–based therapy could fill the need for non-surgical SUI treatments, reducing caregiver workload and healthcare costs by avoiding repeated procedures. Autologous progenitor SMCs are expected to improve moderate to severe incontinence by regenerating sphincter muscle and connective tissue. Using autologous cells minimizes immune risks, and the single in-clinic injection should further enhance safety. If successful, the proposed therapy could regenerate the urethral sphincter, restore function, and offer a safer, practical alternative.
- The applicants are developing an autologous, iPSC derived cell therapy for the treatment of Stress Urinary Incontinence (SUI).
- The applicants intend to use skin biopsies to obtain cells and reprogram them to iPSCs which can be differentiated into pSMCs. The plan is to inject these pSMCs into the urethra of patients suffering from SUI.
- The proposed iPSC-derived cell therapy has strong potential to replace injections of bulking agents and sling surgeries, which are currently the main treatment options for postmenopausal women with stress urinary incontinence (SUI). This therapy may particularly benefit women who have failed previous surgical interventions or who cannot undergo surgery due to age or medical conditions. There is a potential large unmet clinical need.
- The proposal supports an important unmet medical need as a non-surgical option in SUI treatment option especially in light of the recent data that adult muscle biopsy cells are not sufficient to provide therapeutic benefit presumably based on the decline in progenitor muscle population in older individuals.
- A non-surgical curative therapy would greatly improve the standard of care for this SUI. This type of therapy would improve the patient's quality of life and reduce strain on the healthcare system to provide surgical options that are less effective/durable.
- As an autologous, iPSC-derived therapy, this option would be expensive and limited in accessibility at least early on. The cost could be expected to decrease somewhat through automation of manufacturing, which could make the therapy more accessible.
- There is certainly an unmet medical need although the cost of an autologous cell therapy is likely to be high given that each manufacturing run will treat one patient.

Rationale

- Current treatments for SUI provide mechanical support using minimally invasive methods such as synthetic mid-urethral slings and periurethral bulking injections. While considered the clinical gold standard with satisfactory long-term outcomes, these approaches are suboptimal. They do not restore normal urethral sphincter function but instead replace damaged or atrophied tissue with inert materials, often leading to complications such as pain and erosion. There is therefore a strong rationale for developing regenerative therapies. Autologous iPSCs derived from skin fibroblasts offer a promising source for urethral sphincter muscle regeneration in postmenopausal women.
- The rationale is sound and is supported by sufficient preliminary proof of concept data to support evaluation of readiness to conduct IND enabling studies pursuant to pre-IND regulatory feedback.
- SUI is currently treated with surgery to introduce bulking agents or sling surgery to introduce mesh or fascia from the patient. These treatments often fail and secondary treatment is less effective in many patients. In addition some patients cannot undergo surgery because of ongoing medical conditions or age.
- The therapeutic approach aims to use progenitor smooth muscle cells (pSMCs) to replace deficient urethral sphincter muscle and regenerate connective tissue. The pSMCs use the same route of administration (delivery into the urethra) of commonly used but ineffective bulking agents, and skeletal muscle biopsy tissue that was evaluated in clinical trials but did not show efficacy. The skeletal muscle studies demonstrate

that this delivery method can be well tolerated, de-risking the pSMC delivery approach.

- The proposed therapy—autologous iPSC-derived SMCs—aims to restore sphincter function compromised by prior sling procedures, childbirth (the main SUI risk factor), and age-related muscle decline. The proposed injection of cells bilaterally is minimally invasive, avoids anesthesia and operation room use, and is clinically feasible.

- The chronic SUI animal model is appropriate. Immunodeficient Rowett Nude (RNU) rats minimize immune rejection of human cells. SUI induction by ureterolysis (mimicking surgical injury) reduces LPP, while ovariectomy reproduces postmenopausal conditions. Histological analyses confirm urethral damage, including disrupted elastic fibers, validating the model.

- The preclinical rodent model mimics SUI through urethrolysis, which shows a significant reduction in leak point pressure indicating urethral sphincter insufficiency. Histological examination showed that the elastin and collagen fibers were damaged as well. Leak point pressure (LPP) was significantly improved with pSMC implantation back to levels observed in the control animals. There was also a restoration of elastin and collagen fibers.

- The model appears to recapitulate SUI through reduced post-void readouts and also histological analysis. However, although there is a significant reduction, it is unclear how meaningful this reduction is and how it might relate to the human condition. This phenotype can be reversed by treatment with pSMCs, but with only a 20% reduction in LPP to begin with, it is difficult to interpret these data without more background information. Data was presented on long-term engraftment in these animals as well, suggesting that the effect is durable.

- The purity of the product needs to be characterized better for safety.

- The applicants have developed a rat model of SUI and provide data for the impact of transplanting pSMCs into this model. The applicants don't state if the rats are immunocompromised in any way but appear to show long term engraftment. I would have thought that the human cells would be rapidly and vigorously rejected? I can imagine some paracrine effects of the engrafted cells but not long term engraftment.

Project Plan and Design

- The proposed preclinical studies and animal research plan are both necessary and appropriate to advance this project toward IND clearance. They form a critical foundation for demonstrating feasibility, safety, and efficacy before clinical application. Successful execution of the preclinical program is essential for future clinical progress. Clinical development depends on the rigor and outcomes of the preclinical work; therefore, the current emphasis on IND-enabling studies is appropriate.

- The applicant has benefited from detailed comments following INTERACT and pre-IND meeting responses to execute a preclinical development plan to support an initial clinical study.

- The proposed activities are appropriate for effectively progressing this project to IND clearance. Regulatory feedback through an INTERACT and Pre-IND meeting has been integrated into the plans, which is de-risking for the program.

- Further justification is needed to support the study durations for proof of concept and 28-day toxicity studies as well as rationale for dose justification and extrapolation (similar doses are proposed for mice and rats). Immunohistochemistry need to be added to biodistribution per FDA request.

- Engraftment needs better characterization.

- It will be important to determine whether cryopreserved cells will be used in the initial IND or later in clinical development. If not available for initiation of IND enabling studies, bridging studies may be needed to confirm comparability.

- CMC needs to be de-risked further - sorting and purity are concerns.

- CMC activities may require additional time and resource based on FDA feedback.
- The budget and timeline seem reasonable for the proposed activities, with approximately 21 months to finalize the process and complete tech transfer to manufacturing. The nonclinical study timing is consistent with FDA feedback, and allows time for analysis/reporting.
- The applicants have had valuable feedback from FDA. It would appear that they have a lot of work to do as it pertains to CMC. The FDA did not agree with any of the points posited in questions put to them in the CMC section.
- The applicant has outlined process and analytical development activities, however, the cell manufacturing plans in particular will require close attention and careful refinement given the numerous limitations identified, including issues of purity, characterization, and functional validation of iPSC-derived SMCs. Addressing these issues is vital to ensure regulatory readiness and clinical suitability.
- Given the regulatory feedback it is likely that timelines and budgets will be stretched.
- The main risks highlighted are consistent with the development of this type of therapy, namely the risks of failed GMP runs and failed nonclinical studies. For a failed GMP run, the expected timeline shift and contingency costs are captured. The applicant is also using a skilled manufacturing group. Nonclinical execution risk is being mitigated by training staff ahead of the GLP study and having an expert on site for the dosing. It would be helpful to add how the test article is being characterized for this study to mitigate the risk of off-target cell or residual iPSC outgrowth.
- In terms of manufacturing of the cell product the organization has the relevant expertise. My concern is in getting to a place where that expertise is needed.
- I am also concerned that there is a short window of time in which the cells are viable. After a few passages the replication capabilities of the cells drops off very quickly.
- While a potency assay is not required to enter the clinic it is important that the applicants are working towards a potency assay for later stage clinical trials so there is no disruption in development of the product.
- The budget and timeline appear ambitious. While preclinical milestones may be achievable, manufacturing and analytical testing are complex and resource-intensive, potentially requiring additional time and funding.
- FDA feedback indicated that significant steps in the manufacturing process need to be more definitively addressed and these were not included in the development plan timelines or apparently in the proposed budget.
- The risks associated with iPSC-based therapies—particularly around long-term safety, reproducibility, and cell product consistency—are valid and have been identified. The mitigation strategies proposed are reasonable, though contingency plans could be strengthened, particularly around manufacturing bottlenecks and potential delays in regulatory feedback.
- Although access and affordability are briefly mentioned, further planning will be needed to ensure broad patient access. Incorporating cost-effective manufacturing and scalability considerations early in development would enhance long-term impact.
- At this stage, the focus is on demonstrating clinical proof of concept. Because the approach is autologous, the therapy could in theory be broadly accessible in the future and it would make sense to focus more on accessibility after clinical proof of concept.
- Autologous strategy is hard to scale out.

Project Team and Resources

- The team has the appropriate leadership and has brought in external consultants to help support the work. In addition, they will be leveraging the experience and infrastructure of contract manufacturing and contract

research organizations.

- The team has access to the required resources and facilities to perform this work.
- The collective team, including consultants and subcontractors have a demonstrated track record of supporting the development of cell based therapies, with some advisors at >20 years experience in the space.
- The team is well versed in the basic science. I believe they also have animal modeling expertise and they have developed models that mimic SUI.
- The team is well qualified to perform GMP cell manufacturing activities.
- Resources and expertise are sufficient - importantly, consultancy in manufacture.
- Strong team.
- I am concerned that they don't have the expertise needed to adapt the manufacturing process to GMP conditions.
- A secondary concern is being able to develop a GMP compliant manufacturing process that is cost effective. That is tricky in an autologous setting.
- The team is well-qualified and appropriately structured to execute the proposed work. Leadership brings internationally recognized expertise in stem cell biology, molecular research, and clinical studies. The group is supported by experienced consultants and subcontractors, some with over 20 years in cell therapy development, and will leverage contract manufacturing and research organizations. They also have access to the necessary facilities and infrastructure to conduct preclinical, manufacturing, and analytical activities, though additional details on regulatory-grade readiness would strengthen confidence.
- The project plan is well organized, covering preclinical studies using a rat model of SUI with human iPSC-derived SMCs, toxicology testing in mice, and GMP-compliant manufacturing protocols. The use of iPSC mRNA reprogramming (uBriGene kit) is innovative but lacks independent validation, raising concerns about reproducibility and feasibility. Moreover, the clinical protocol remains undefined and contingent on preclinical outcomes, adding uncertainty to translation.
- The team has strong credentials and relevant experience, but the absence of independently verified data for the reprogramming platform and limited clinical planning present key risks to feasibility. If these challenges are addressed, the project has potential to yield a novel, clinically relevant therapy for stress urinary incontinence
- The team appears to be replete with appropriate expertise to manage the timelines and address any CMC deficiencies outlined by FDA.

Population Impact

- This study advances women's health by developing regenerative therapy for aging women with unmet need. SUI is a common pelvic floor disorder affecting up to half of postmenopausal women worldwide. By age 80, one in six women will undergo SUI surgery, and incidence is expected to rise with aging populations. This proposal targets older women with recurrent SUI after prior anti-incontinence surgery. The therapy uses autologous iPSC-derived pSMCs from patient dermal fibroblasts, avoiding the need for muscle biopsy. Previous trials using primary muscle-derived cells showed safety but limited efficacy, highlighting the need for a regenerative approach. No current therapy regenerates the urethral sphincter with SMCs, making this approach novel. To address safety concerns of iPSC-derived cells (potential tumor formation), the applicant proposes toxicology studies before clinical application.
- This has the potential for a high unmet clinical need with no alternative therapies that do not require ablation, surgery etc. The strategy is particularly suited for older patients, as it bypasses the need for muscle biopsy. Women with incontinence often limit social and physical activities, which may lead to isolation, depression,

and reduced exercise. Reported prevalence ranges from 14% to 50%, with SUI being two to three times more common in women than in men. Patient advocacy groups are strong in California with significant outreach to patients to ensure good enrollment and engagement in this potential therapy.

- The applicant described the causes of SUI, the reasons why this type of therapy could be adopted, and the demographic group affected (elderly women).
- The goals for enrollment in California do address a broad range of ethnic groups with Black, White, Hispanic and Asian subjects all targeted for enrollment.
- There is a disproportionate number of post-menopausal women who suffer from SUI and they will be well represented in the clinical trial.
- Proposal will benefit from clinical sites experience with intended population in similar trials in SUI.
- Important target with broad needs.
- There is limited discussion on the potential safety risks of iPSC-derived therapies, such as potential tumor formation and how this will be monitored and addressed clinically if there are issues.

Application #	PDEV-19139
Title (as written by the applicant)	Develop a human iPSC-based cell therapy for Canavan disease (CD)
Therapeutic Candidate (as written by the applicant)	Human iPSC-based cell therapy
Indication (as written by the applicant)	Canavan disease (CD)
Unmet Medical Need (as written by the applicant)	Canavan disease (CD) is a rare, fatal neurological disorder. There is neither a cure nor a standard course of treatment for this disease. Treatments are symptomatic only. Therefore, it is urgent to develop therapeutic strategies that could lead to effective and long-term therapeutic effects.
Major Proposed Activities (as written by the applicant)	• Completion of IND-enabling studies • Obtaining IND clearance • Performing clinical trial start-up activities
Statement of Benefit to California (as written by the applicant)	California is estimated to have ~12% of all cases of Canavan disease (CD) in the U.S. Besides the emotional and physical pain this disease inflicts on families, it produces a medical and fiscal burden in California that is larger than any other states. The proposed therapeutic candidate will represent great potential for both California patients and industry. It would also help to maintain California's leading position in clinical developments by creating safe and effective stem cell-based therapy.
Funds Requested	$4,393,300
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	81
Median	85
Standard Deviation	8
Highest	90
Lowest	60
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	9
(1-84): Not recommended for funding	5

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to

indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

Key Strengths and Weaknesses

- Strengths: Compelling data from a mouse model with fibroblasts as the starting material. The application shows a generally good understanding of genetic and environmental factors regarding this disease. The proposal includes good outreach to patient groups for their opinions.
- Weaknesses: Patients likely won't improve in symptoms. This technology (NPCs) has not been shown to successfully treat any neurologic disease. The applicants have completely switched starting material with no pilot data showing that they can accomplish what they say they will with PBMC. That said, the pivotal experiments will be repeated for the IND package regardless and they will be given a chance to demonstrate effectiveness.
- The target indication is an ultra-rare disease with competing therapies. The translation of treatment in mice to treatment in human will be difficult in terms of both location and dose.
- The team has a less than ideal track record in this disease. The PI of the study has limited publications in Canavan disease. This reviewer is surprised given the potential revolution in therapy which is proposed. The collaborating neurologist does not have a track record in Canavan disease.
- This is a novel approach with an autologous iPSC-derived neural progenitor cell genetically modified via lentivirus to produce aspartoacyclase to treat Canavan disease. While the impact could be high if effective, this will be a very difficult product to manufacture and requires a complicated surgical procedure for delivery.
- The applicants present the combined cell and gene therapy approach over gene therapy alone. However, peer-reviewed literature indicates that other clinically-tested gene therapies BBP-812 (BridgeBio), and MYR-101 (Myrtelle) have proven clinical benefit.
- In a phase 1/2 open-label clinical study, a significant decrease in N-acetyl aspartic acid (NAA) was observed showed significant reductions in NAA and improvements in motor function in all of the patients (N=11). This study has since been published.
- The risk/benefit must factor in costs for a combined cell and gene therapy, other therapeutics available, and the clinical advantage over other applications.
- It is unknown what the cost will be for this product, though it will be expensive. The applicants note that the product they are developing is one-time use, which is different than that of an AAV-based therapy, which may require several infusions over a patient's lifetime.

Value Proposition

- The project has a borderline value proposition.
- The applicant proposes an autologous iPSC-derived neural progenitor, gene modified to express aspartoacylase to treat Canavan disease (CD). CD is a rare, autosomal recessive neurodevelopmental disorder. While the impact could be high if effective, this will be a very difficult product to manufacture and requires a complicated surgical procedure for delivery.
- This proposal seeks to address the unmet clinical need in Canavan disease, an ultra-rare, autosomal recessive neurodevelopmental disorder. Disease progression is caused by aspartoacylase enzyme A deficiency (known as ASPA), which is associated with accumulation of acetylaspartic acid in the brain, plasma, urine, and CSF.
- Two alternative gene therapies exist to lower acetylaspartic acid and have shown significant clinical efficacy. Hence, given the rare disease, alternative therapies that lower the critical enzyme associated with disease progression, and significant costs to develop a combined cell and gene therapy as proposed, the value

proposition is somewhat lower.

- There is currently no cure for Canavan disease, and individuals with this disease typically die at a young age and with significant physical and mental disabilities. This treatment, if successful, would provide a meaningful and substantial improvement in clinical outcomes. Treatment early would have the most significant benefit.
- Canavan disease is a significant unmet medical need, as there is no cure and available treatments only mitigate symptoms. Affected individuals typically die by age 10, and during their lifetime, they require significant effort from caregivers and the health system. A successful treatment would be transformative for affected individuals, especially if treated early.
- There are two other gene therapy clinical trials (Myrtelle, Inc. and Aspa Therapeutics) both utilizing AAV to transfer the aspartoacylase (ASPA) gene into the brain. Myrtelle, Inc., has completed a phase 1/2 open-label clinical study and published an article on the trial. The study showed a significant decrease in N-acetyl aspartic acid (NAA), showing that ASPA is being expressed. Aspa Therapeutics reported in October 2024 that the 11 participants in the low-dose cohort all showed significant reductions in NAA and improvements in motor function. Given the results of these two studies, it would be challenging for this project's therapy to be more accessible and/or affordable compared to these products.
- If this therapy were the first approved, it would be well-received by the Canavan patient community and the healthcare system.

Rationale

- Data on patient blood lymphocytes are required to support the rationale.
- The scientific rationale appears sound with supportive preclinical data from mouse models. The manufacturing has been well developed with good feedback from the FDA pre-IND meeting.
- A number of mouse model experiments showed increased NAA activity and decreased vacuolization in the brain following cell injection with a sustained presence of cells for up to six months, with improvements in myelination and motor function. The scientific rationale indicates the therapy has potential to be clinically effective. However, the MOA is unclear given the effectiveness of other gene therapy targets.
- The scientific rationale of this project is sound. Developing drugs for conditions/diseases where there are no available therapies and patients have a very poor prognosis provides many regulatory advantages due to the risk-benefit ratio. And the therapeutic approach and route of administration are sound, as the cells must be located in the brain if the condition is to be reversed.
- The preclinical data in a Canavan disease mouse model show that the therapy has the potential to be successful.
- Using disease models is often the best way to demonstrate the potential success of the proposed therapy. The strength of this model lies in its demonstration that aspartoacylase is expressed, resulting in a lowered level of N-acetyl aspartic acid.
- This product is unlikely to improve patients symptomatically due to the advanced stage when patients are often diagnosed.
- The applicants argue that this will be more affordable than an AAV approach. There is no other model like the one proposed, so no comparison can be made. It's not clear that payers will reimburse any such patient with Canavan disease for this therapy, especially given the extensive neurosurgery that needs to happen.
- As far as potential risk to patients, this would be the most invasive therapy brought to Canavan disease as it involves multiple protocols with the injection of stem cells into the brain.
- As part of their rationale, the applicants mention that PMD has been treated with NPCs. However, the

reference discusses long-term safety after five years of follow-up, not efficacy data.

- Cell delivery may be a hurdle, as the applicants plan multiple burr-holes at three depths to deliver the planned number of cells per subject.

Project Plan and Design

- A caveat to the experimental data is that it's not clear what the mechanism of disease is, nor what the cells are when they are injected into the mouse brain. This impacts the rationale and a critical component. Essentially, the therapy is cells processing a buildup of NAA. It's not clear that NPCs are required to do this - possibly, any cell type could do that. This is an unknown in this application. In fact, it's not clear that the cells that were injected were characterized, so it's not clear what kind of cells they became or if they just stayed as NPCs in the brain.

- One of the largest limitations that the applicants have so far used CD fibroblasts, and now for their clinical product they are moving to blood samples, which is an entirely different starting substance. This may be a fatal flaw to this application - it lacks pilot data to show that a PBMC can be reprogrammed into IPSCs as they describe.

- One critique of the applicants' reimbursement landscape analysis is that they are going to review payer policies from Medicare and private payers. However, 50% of children are on Medicaid or on CHIP insurance in the United States, so that's where to focus. The manufacturing plan outline is given, including testing for safety, genetic stability, NPC testing, viability testing, etc., followed by purity testing.

- Another critique is that the stage of disease to be treated is unclear. Most of the time, patients are very advanced with this disease when they are diagnosed, and likely no therapy is going to allow for improvement. This will be the case until newborn screening is derived for this disease. This lessens the value proposition.

- No CRO will be used in the conduct of the proposed clinical plan (a benefit in this reviewer’s opinion).

- The manufacturing plan is well designed with appropriate reagents, analytical methods and release methods proposed. The primary concern is the complexity of the manufacturing process and the autologous nature of the product, adding variability to the success rate.

- Based on resistance of donors to provide fibroblast (skin samples), a paradigm shift in the project plan to generate iPSCs from PMBCs may prohibit advancement of the program. The time taken to generate the product (lentiviral transduction takes 93 days) could be rate-limiting.

- Potential disparity in timing and in which patients would be eligible for and responsive to the therapy based on clinical prognosis - would there be clinical benefit for patients with advanced disease?

- The investigators have had multiple meetings and communications with the FDA, and it is clear what additional preclinical and manufacturing activities must be completed for the IND.

- The proposed budget has very specific costs for preclinical and CMC activities, which appear derived from actual quotes from CMO/CROs that would be performing these activities (however, since quotes were not included, it is not possible to verify). The three objectives set forth for this grant - complete IND enabling studies, obtain an effective IND, and prepare for clinical start-up - should be feasible with this budget.

- The risks to achieving objectives for this grant have been mitigated by the extensive meetings and correspondence with the FDA.

- The applicant has requested funds for access and affordability planning and for market landscape analysis.

- Low enthusiasm for the potential impact of this particular disease target.

Project Team and Resources

- The personnel have the appropriate expertise and resources.
- The applicant and associated team have significant expertise to advance the program to an IND. In addition, preclinical, GMP manufacturing, analytical, and regulatory activities will all be outsourced.
- The team has the leadership, expertise, and staffing plan to get an effective IND successfully. Much of the key non-clinical, GMP manufacturing, analytical, and regulatory work will be done by outside CMO/CROs with the appropriate expertise. This use of outside expertise is not uncommon for academic teams doing drug development.
- This project has been in the works for multiple years, which is not surprising given the other demands of academic investigators. But the team does seem to be primed to complete the work for an IND.
- From their work to date, it would appear that the team is capable of moving this project to a clinical trial.

Population Impact

- The application shows a generally good understanding of genetic and environmental factors regarding this disease. The demographic groups are impossible to study as this is an ultra-rare disease. It is unlikely that many Californian patients will be treated. There are also multiple competing interests.
- Patient perspectives have been assessed, which is how the applicants decided to use peripheral blood instead of fibroblasts.
- This is a rare disease so limited population impact data are available.
- Given the ultra-rare disease, it is unlikely that the various demographic groups could be meaningfully factored into an analysis.

Application #	PDEV-19168
Title (as written by the applicant)	Epigenetic Gene Therapy for CDKL5 Deficiency Disorder (CDD)
Therapeutic Candidate (as written by the applicant)	A gene therapy based epigenetic editor to treat CDKL5 Deficiency Disorder (CDD)
Indication (as written by the applicant)	CDKL5 Deficiency Disorder (CDD; OMIM 300203; ICD G40.42)
Unmet Medical Need (as written by the applicant)	The only approved intervention for CDKL5 Deficiency Disorder (CDD) is ZTALMY, a neuroactive steroid that can reduce seizure burden. There are no targeted therapeutics aimed at restoration of endogenous CDKL5 making the proposed product a highly impactful therapeutic intervention.
Major Proposed Activities (as written by the applicant)	• Preparation and conduct of a pre-IND meeting with the FDA with optimized therapeutic following dose-finding efficacy and safety studies. • Completion of IND-enabling studies through GMP manufacturing and large animal dose and safety studies. • Clinical protocol development in anticipation of a phase 1/2 trial for CDKL5 deficiency disorder
Statement of Benefit to California (as written by the applicant)	There are 40-60 girls in California currently diagnosed with CDKL5 Deficiency Disorder (CDD) with up to 400 girls anticipated based on the population of California. The financial and emotional burden on the children, families, and caregivers is immense. The proposed therapy could provide a large effect on the qualify of life for those suffering from CDD. Additionally, several new employees will be hired to contribute to the development of this therapy, recruiting talented new researchers to California.
Funds Requested	$12,969,829
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: 82

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	82
Median	82
Standard Deviation	3
Highest	85
Lowest	75
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	3
(1-84): Not recommended for funding	10

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

Key Strengths and Weaknesses

- This reviewer's score was based on manufacturing risks for a single AAV with multiple guide RNAs, and a borderline value proposition.
- The key strength is the rationale and potential to treat many other X-linked diseases. The key weakness is that the core technology, i.e., a single vector administration of an epigenetic editor, has not been demonstrated sufficiently to warrant both early and late stage funding. The team should first demonstrate that the single vector system can package the editor cargo and the necessary gRNAs and lead to gene reactivation equivalently to the dual vector system. In addition, a comparison to gene replacement approach should be considered *in vivo.*

Value Proposition

- The proposed therapy addresses a rare disease without any suitable treatments. The prior evidence that gene upregulation can be impactful in this disease after the onset of symptoms is especially promising. In addition, the platform potential for this therapeutic approach to address a broad spectrum of X-linked disease is also very appealing. Once the core vector, payload and delivery aspects have been established for CDKL5 Deficiency Disorder (CDD), initiating new therapeutic programs could consist of gRNA discovery and optimization. There is momentum at the FDA and in the community broadly to adopt this kind of platform approach for rare disease, and the project described in this application is a great example of that kind of opportunity.
- CDKL5 deficiency is a severe neurogenetic disorder that causes seizures (often intractable) and developmental delay, there are no treatments that currently target the specific disease molecular mechanism.
- While there has been concern in the past about how reversible the neurologic deficits would be, there is now substantial data showing that post-natal treatment can have a significant positive effect.
- These patients have a high burden of medical care due to the developmental delays and seizures (sometimes even requiring mechanical ventilation, etc.) so a successful treatment would be more accessible and affordable. Due to this high burden of care, this reviewer anticipates that patients and families will have a very high level of uptake for this therapy.
- This is a project that continues the translation of previous CIRM award, but has not yet been presented to the FDA (INTERACT/Pre-IND) to use their therapeutic candidate to demethylate CDKL5, therefore activating the unaffected allele on the X chromosome that has been inactivated (through methylation).
- High unmet need; while there is existing therapy, it does not address all manifestations of disease and is high-cost.
- The applicant notes numerous other investigational gene therapies under development; while applicant describes value proposition of their proposed approach, given the stage of their development and rarity of disease, speed may be a factor and complicate development unless they can accelerate efforts (i.e., they're very early in development).
- There is a complex landscape with other AAV products in development.

Rationale

- Programmable transcription and epigenetic reactivation of CDKL5 is an interesting therapeutic approach. The scientific rationale is supported by scientific literature and the applicant's own research.
- This reviewer strongly supports the proposal to move to a single vector system and in fact would encourage the applicant not to consider moving forward with a therapeutic with the dual vector system. There is no reason to believe the single vector system cannot lead to equivalent epigenetic reactivation but of course the devil is in the details. Determining if the cargo can be efficiently packaged in a single vector and lead to sufficient reactivation is a necessary first step before other work.
- There is excellent preclinical data generated with a previous grant showing that not only is there substantial epigenetic editing, but that there is functional correction, plus additional work defining the mechanism to be corrected. Two published studies were found especially compelling as foundational robust preliminary data.
- Model systems will be in both mice and large animal models - one limiting issue is that there is a human-specific isoform of CDKL5 (CDKL5115), which contains unique exons (19–21) that are not present in other large animal models, so it would never be possible to model that *in vivo* (although the team has done preclinical work in human brain organoids).
- This represents a complex objective - this reviewer is uncertain how X-Inactive Specific Transcript (XIST) is silenced and why other genes remain un-reactivated. Off-target profiling needs to be done more thoroughly with the drug product.
- Direct comparison with AAV over-expression needs to be done to establish the value proposition.

Project Plan and Design

- Well-designed project, though early stage.
- Preclinical work will likely need to be redone with the drug product.
- This reviewer thinks it would be wise for the team to utilize the animal studies described in Preclinical Activity 2 to better characterize which cell types are transduced and which show an increase in CDKL5 expression. This seems like an essential piece of information to have before moving on to Preclinical Activity 3.2 where one arm of the large animal study is devoted to intrathecal (IT) delivery. The brain regions and cell types reached by intracerebroventricular (ICV) and intrathecal (IT) are very different and a better characterization of what cell types are contributing to the functional recovery observed in mice could help inform the large animal study. In addition, a good understanding of which cell types are transduced will help inform off-target studies.
- The primary endpoint is 30% reduction in major motor seizure frequency, which has previously been used for the one approved treatment for CCD.
- AAV9 vectors have a relatively well-established transduction profile for neurologic disorders across ages and delivery methods (systemic, IT, ICV, etc.) They have identified the team performing the studies and they have sufficient expertise to perform procedures.
- The budget and timeline are both appropriate, the team has been thoughtful about "pinch points" in the process and accommodating them.
- This reviewer might usually question the need for large animal models for a vector that's already been well-studied in various large animal models; however, given that we know less about the efficacy that's needed for this more complicated epigenetic remodeling, it is appropriate. This is especially important as there may be significantly different dosages in different cell types within the CNS, or even transcript-level differences when modulating the promoter in this way.

Project Team and Resources

- This appears to be a good team with appropriate personnel and support.
- This is strong and productive team - there are no concerns.
- The team seems appropriate for this stage of development and seems to take advantage of the robust network of drug development and clinical resources within the university system.
- This reviewer appreciates the inclusion of an expert in biomarkers and clinical trial readiness specifically in CDD.
- The time frame for adverse effects is especially important as there is always a concern for off-target activation/repression with this therapy that might not be immediately evident.
- The applicants have a specific trigger for conducting the INTERACT meeting. This is important to define ahead of time as it can often get pushed forward or back for non-scientific reasons.
- This reviewer would have liked to see different types of organoid differentiation (e.g., dorsal and ventral forebrain organoids). It's hard to balance the reproducibility of more directed differentiation with more clinically-relevant undirected cerebral organoid, so this reviewer would like them to speak a bit more about their decisions in that realm.
- This reviewer would also like more clear guidance around decision making balancing multiple priorities for the single or dual vector decision.
- The institutional neurology clinical trials unit and clinical team are well-trained and appropriate for the study.

Population Impact

- Good analysis of impact - no concerns.
- The application has two letters of support from patient-focused groups. This reviewer especially appreciates the proposal to include a member from one of these groups on the program Executive Committee to provide close contact with the patient community, which will be essential to educating them about this therapeutic option.
- Good engagement with a patient advocacy group and a family foundation.
- Impressed the team included multi-lingual aspects, including medical interpretation of all study documents into any language as needed.

Application #	PDEV-19136
Title (as written by the applicant)	IND-enabling activities for a gene editing therapy for Duchenne muscular dystrophy
Therapeutic Candidate (as written by the applicant)	A gene editing therapy that permanently removes mutations in a hotspot region for Duchenne muscular dystrophy (DMD) patients
Indication (as written by the applicant)	Duchenne muscular dystrophy
Unmet Medical Need (as written by the applicant)	Duchenne muscular dystrophy is a fatal disease with no cure. There are currently only limited approved therapies that have not demonstrated significant benefit in pivotal or confirmatory trials to date. Thus new therapies are needed, especially ones that target the underlying cause of disease.
Major Proposed Activities (as written by the applicant)	• Manufacturing scale up and analytical development • Completion of IND-enabling studies • Submission of an IND application
Statement of Benefit to California (as written by the applicant)	Here we will develop a gene editing therapy for Duchenne muscular dystrophy to IND filing to start clinical trials. Duchenne affects ~600 patients in CA leading to progressive muscle weakness and premature death in the 20-30s. There is no cure and only limited approved therapies that are not highly effective. Thus our approach would offer a novel treatment to fix the underlying cause of disease for half of Duchenne mutations aiming to save the lives of CA patients and reduce healthcare costs.
Funds Requested	$7,500,000
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: 81

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	80
Median	81
Standard Deviation	4
Highest	84
Lowest	70
Count	12
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	12

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel’s discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in

the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

Key Strengths and Weaknesses

- Key strength is novel approach to potentially provide a single, one-time treatment; weaknesses are the overall complexity in a dual vector system regarding co-transduction, targeting, cost, and safety.
- Approach - Using two AAVs packaging Cas9 and gRNA respectively to edit DMD such that there's a deletion of exons 45-55. Overall, the strategy is good since exons 45-55 deletion would create a highly functional dystrophin.
- Targeting between 0.1% and 1% cleavage and rejoining of the dystrophin gene with exons 45-55 excluded. This is small.
- AAV doses used are extremely high - doses used in mouse studies with humanized dystrophin gene are up to 2E14 vector genomes/kilogram (vg/kg) which means that actual AAV9 doses are double. This creates a big safety risk.
- Concern that the kinetics around the inactivation of Cas9 will be a challenge since the dual AAVs are given at the same time. If the guides inactivate the Cas9 too quickly, the amount of cleavage leading to NHEJ will be too low.
- Translational concern - FDA has asked the applicant to use a specific, relevant preclinical model for toxicity and biodistribution studies. This reviewer thinks the applicant should try to use surrogate guide RNAs to get gene editing in the model's relevant tissues. Doses proposed are very high (up to 3E14 vg/kg). The applicant should assess complement activation, DRG toxicity, cardiac toxicity etc. in the recommended preclinical model as well. Translatability is a risk for this approach since large animal studies have not been done.
- The proposal says that dose will be translated from mouse to humans directly per body weight conversion. That will put the clinical dose at 3E14-4E14 vg/kg. That dose is very high, and it creates a safety risk.
- FDA has asked the applicant to do GUIDE-seq based off-target analysis in all relevant tissues. This will be an important experiment to rule out off-target toxicity from tissues with high AAV tropism.
- The applicant wants to dose younger patients. It is unclear if satellite cells are edited. This is critical since dystrophin is important in asymmetric division of satellite cells (maintaining the satellite pool and also creating muscle cell progenitors to fuse and repair damaged muscle).
- The dilution of vgs over time cannot be accurately answered in sedentary mice 4 months after dosing. The mice will need regular exercise periods to ensure some muscle regeneration.
- Very heavy immunosuppression regimen consisting of sirolimus, rituximab and prednisone.
- CMC - Each AAV vector needs to be made separately and QC'ed. A 10 kg patient would get 2E15 vgs of each vector (2E14 vg/kg). One 200L batch would treat 10 patients if the yield is 2E16 vgs. COGs will be high.
- CMC plans appear acceptable.
- High dose level and inefficient approach raise safety concerns and manufacturability concerns (high cost of goods).
- Safety risk for low efficiency deletion with dual AAV is a serious concern.

Value Proposition

- Proposed therapy, if successful, would offer significant value.

- DMD continues to be associated with high morbidity and mortality with urgent unmet medical need for new therapies; many promising investigational therapies under development.
- Safety risk involving dual AAV lowers value proposition.
- Approved gene therapy exists to treat a broader population with DMD; however, this approach intends to permanently correct the mutation for a potential lasting treatment. This reviewer suspects efficacy to be similar as it is subject to number of cells transduced (like current treatment) and stem cells are difficult to transduce. Safety could be improved as it has the potential for less treatments, butoff target editing is possible. Therapy will be expensive (similar to or higher than approved therapy due to dual vector), but cost can be reduced if a single dose therapy. Precedent set for gene therapy use in the field thus clinical data will drive uptake.
- ~5000 appropriate DMD patients in the US. But the very inefficient editing until very high vg doses is concerning.

Rationale

- Proposed gene therapy approach underpinned by very robust nonclinical development program that has generated promising proof-of-concept and pharmacology data; supportive data are compelling and the applicant is at an appropriate stage for translational work.
- Extensive discussions with FDA on nonclinical development program have been productive, engaging, and largely positive.
- Some potential safety concerns due to the magnitude of proposed doses that are planned; doses appear to be in a range where there have been strong and serious adverse clinical safety signals; this is reflected in the comments from the FDA regarding required nonclinical studies (study design, duration, number of species and studies requested).
- Heavy immunosuppressive regimen is a concern.
- Serious safety risk for high vector doses since the efficiency is low.
- Sound scientific rationale with key concerns being dual vector use/co-transduction, adverse events with system delivery, poor repeat dosing ability, delivery to large number of target cells, ability to target stem cells, and safety of off-target editing. Precedent established for use of gene therapy and gene editor; supportive animal data; risk of dual vector approach for safety and efficacy (due to dose and ability to co-transduce cells).

Project Plan and Design

- Project plan and design is excellent.
- Plans appear reasonable, robust, and intentional; underpinned by extensive interactions with the FDA and a lot of development work to-date that has generated good understanding of product.
- Plan, budget, and timelines appear reasonable; relevant preclinical model study is not over-designed and balances scientific need, regulatory requirements with cost considerations and animal welfare concerns.
- Self-inactivation is a good strategy, but it needs to be packaged into a single AAV.
- Plan is to manufacture at small scale thus technically enabling an IND, but it will require significant funds shortly after IND approval to resupply the clinical trial. No or understated drug product development funds delineated (only formulation shown). Dual vector will require drug product (DP) development beyond that for a typical vector for a single DP or for bed-side formulation. Overall, not much information for CMC development, and it's uncertain what has been already done.

Project Team and Resources

- A good team, particularly on the regulatory side.
- Project team and resources are excellent.
- Consider postponing the planned Pre-IDE meeting on the AAV9 antibody assay.
- Solid corporate team - no concerns.
- Team is primarily in the research space; great CMC consultant and great board adviser with FDA experience; limited full-time industry or business experience; relatively new CRO with good depth; good CDMO.

Population Impact

- Significant population impact.
- Population impact is valuable.
- Adequate impact - if it works.
- There is an existing approved gene therapy; however, concerns exist with that therapy. This therapy may treat a smaller population, but can be more efficacious. It will be a challenge for this to be a financially accessible therapy, as it requires large doses for systemic delivery; if repeat dosing is required, this will posed a significant challenge.

Application #	PDEV-19132
Title (as written by the applicant)	Preclinical Development of Targeted siRNA Nanoparticle Therapy for Autosomal Dominant Polycystic Kidney Disease
Therapeutic Candidate (as written by the applicant)	A kidney-targeted peptide amphiphile micelle delivering siRNAs against TMEM16a and MCP1 to reduce cyst growth and inflammation in ADPKD.
Indication (as written by the applicant)	Autosomal dominant polycystic kidney disease (ADPKD), the most common inherited kidney disorder, affecting over 13 million people worldwide.
Unmet Medical Need (as written by the applicant)	Current ADPKD therapy (Tolvaptan) offers limited efficacy and causes frequent adverse effects. Our targeted siRNA approach aims to safely and effectively slow disease progression, reduce cyst burden, and preserve kidney function.
Major Proposed Activities (as written by the applicant)	• Conduct IND-enabling CMC, pharmacology, PK/BD, and GLP toxicology studies. • Hold pre-IND meeting with FDA and incorporate feedback into regulatory package. • Prepare and submit complete IND application for first-in-human ADPKD trial.
Statement of Benefit to California (as written by the applicant)	This project will advance a first-in-class, targeted gene-silencing therapy for ADPKD, a serious genetic kidney disease affecting thousands of Californians. By slowing disease progression and delaying the need for dialysis or transplant, the therapy could reduce healthcare costs, improve patient quality of life, and create high-value biotechnology jobs in California through local research, manufacturing, and clinical development.
Funds Requested	$10,704,857
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	80
Median	80
Standard Deviation	4
Highest	85
Lowest	70
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	2
(1-84): Not recommended for funding	11

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel’s discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

Key Strengths and Weaknesses

- Strengths include the tremendous unmet need for this relatively common genetic disorder; the strength of the data shows good collecting duct (CD) targeting and therapeutic effect.
- Weaknesses include the question of appropriateness and predictive value for therapeutic success in humans of the mouse model used to test the drug and the possibility of off target effects, given that the drug also targets the liver.
- The proposed therapy has the potential to benefit all genetically confirmed ADPKD patients, regardless of demographic background by providing a targeted, non-invasive treatment option that does not require complex surgical intervention or hospitalization.
- Stellar pharmacokinetics (PK) and pharmacodynamics (PD) are needed to achieve the desired risk:benefit ratio.
- There's concern regarding the utility of targeting MCP1 in the context of autosomal dominant polycystic kidney disease (ADPKD). While there's enthusiasm about TMEM16a/Ano1, this target could be disease modifying without adding significant risk by targeting MCP1.
- The authors put together a good application with good details on the pre-clinical efficacy validation, PK, safety/toxicology, CMC and and GMP manufacturing.
- The team has appropriate expertise except for over-allocation of the CEO's effort.
- The lack of adequate validation for the collecting duct targeted vs non targeted particles in both in vitro and in vivo studies, coupled with the fact that the applicant did not provide key pieces of in vivo proof of concept (POC) data in disease relevant models significantly decreased enthusiasm and is a score driver.
- Serves a large, unmet clinical need. There is no approved therapy that addresses both cyst growth and the underlying inflammatory processes driving disease progression.
- Overall, the nonclinical data presented indicate proof of concept for the therapy and nonclinical therapeutic target in appropriate in human in vitro and animal models designed to recapitulate ADPKD.
- Careful consideration of time commitment is advised; 100% effort is expected of the company CEO, who oversees multiple other projects and company personnel.

Value Proposition

- Effective drugs for ADPKD are a major unmet need. The standard of care Tolvaptan is very expensive, provides only modest reduction in cyst formation and has multiple side effects with poor patient adherence. Effective cyst reduction and preservation/restoration of renal function would dramatically improve patient health and lower costs of end stage renal disease (ESRD) seen in subjects with ADPKD by age 50-60. Necessity for dialysis or renal transplantation would be sharply reduced, lowering morbidity and mortality and overall health care costs. The proposed therapy has the potential for rapid uptake by the affected population given the dire prognosis of ADPKD as currently treated.
- This therapy's reduced dosing frequency and predictable administration schedule will improve adherence compared to Tolvaptan. The value proposition is that this therapy, if effective, has the potential to treat patients with both types of mutations for ADPKD upon genetic testing, reducing disease potential/progression in thousands of patients over the standard of care, thus providing a practical approach to treatment for patients while reducing high frequency caregiver oversight and reduced burden on the healthcare system.
- Stellar PK/PD are needed to achieve the desired risk:benefit ratio.
- The projected cost is expected to be significantly lower than biologics requiring complex handling or genetic

engineering, making it more accessible to patients and payers.

- Overall this is a relatively strong application. Nevertheless, concerns regarding the specific targets and safety concerns around chronic inhibition, lack of strong evidence in support of CD-targeting and the lack of stronger in vivo validation data, significantly dampens enthusiasm for the application.

- Value Proposition Strengths:

    - The proposed therapy relies on pairing kidney-targeted delivery with dual siRNA silencing of two downstream drivers of cyst fluid secretion and inflammatory amplification. If the mouse and patient-cell data translate, the approach could potentially slow cyst expansion, reduce kidney size growth, and stabilize or improve renal function with an intermittent outpatient infusion schedule rather than a daily oral pill that carries a high symptom burden.

    - Relative to Tolvaptan, the therapy has a plausible path to better efficacy:tolerability balance and a lower day-to-day burden for patients and caregivers.

    - Manufacturing based on synthetic lipids, peptides, and siRNA should be more scalable and potentially more affordable than viral vectors or cell-based products, aiding future access.

    - The plan's emphasis on biodistribution, repeat-dose safety, and durability of knockdown is appropriate to potentially demonstrate that kidney targeting is robust enough to justify chronic use.

    - The program's success will hinge on validating a dosing interval that is both durable and convenient and on generating early human signals on total kidney volume and eGFR slope that are similar or exceed contemporary benchmarks.

- Value Proposition Weaknesses

    - The data presented by the authors is not supportive enough regarding CD targeted biodistribution and it's superior efficacy vs. non targeted particles.

    - Chronic inhibition of the candidate's two targets is a big concern given the risk-benefit profile deemed appropriate for an ADPKD therapy.

    - The precise collecting duct targeting mechanism is unclear from the use of the applicants terminology. The applicant calls this CD or CD3.

    - Cysts that are not connected to the rest of the nephron anymore, where no drug will be taken up via filtration, are not considered. The reviewer strongly suggests the use of the WS25/- model to test this hypothesis. This is focal model where cysts form and separate from the nephron and is the closest mouse model to human ADPKD.

    - Preliminary data in a slow-progressing model would be necessary to to support the approach.

    - TMEM16A is broadly expressed outside the kidney. Systemic knockdown could plausibly affect multiple organs. If micelles leak systemically or accumulate in liver or lung; these are on-target toxicities, not off-target. TMEM16A is not the only chloride pathway in kidney cysts. Pathway redundancy may blunt efficacy.

    - The field has seen mixed outcomes with CCR2/CCL2 blockade in other diseases, and chemokine network redundancy may compensate for the CCL2 suppression, diminishing efficacy over time. Also, macrophages also mediate tissue repair after acute kidney injury**.** Chronic CCL2 suppression could worsen outcomes after intercurrent renal insults (such as contrast, ischemia, sepsis).

    - Dual-siRNA adds benefit potential, but it also doubles the on-target risk potential. It also complicates dose finding if the therapeutic window for one target is narrower than the other.

    - ADPKD patients already have higher UTI rates; systemic leakage of the nanoparticle cargo could

tip the balance toward recurrent infections.

- Cationic/PEGylated nanoparticles and some oligonucleotides cause proximal tubular vacuolization or low-grade proteinuria with repeat dosing. Blinded kidney histopathology beyond cyst metrics, kidney injury biomarkers (KIM-1, NGAL), and electron microscopy in GLP toxicology studies should be included.

- The grant text alternates between use of “encapsulation” and “covalent linkage” of siRNA to PEG. These are fundamentally different products with different release/potency/PK and safety expectations.

Rationale

- The applicant provides strong evidence for the scientific rationale and therapeutic approach. The proposed therapy address two downstream consequences of loss of PKD gene function: a) increased expression of a chloride channel, TMEM16a, which leads increased fluid secretion into cysts and cyst enlargement; b) increased expression of MCP1, a monocyte chemoattractant, which causes increased proliferation of cyst lining cells and infiltration with proinflammatory macrophages.

- The biological rationale is coherent overall and supported by orthogonal pieces of evidence. TMEM16A/ANO1 contributes to chloride-driven fluid secretion, epithelial proliferation, and ciliary dysfunction in cyst epithelium, while MCP1/CCL2 orchestrates monocyte–macrophage recruitment and a pro-cyst inflammatory milieu. Dual targeting may address both a proximal driver of cyst expansion and a sustaining inflammatory loop, increasing the chance of disease modification compared with single-mechanism approaches. The micelle platform is sized for renal access, displays a collecting-duct–targeting peptide, and has prior in vivo experience showing kidney tropism, low immunogenicity on repeat dosing, and durable delivery of short RNAs in other models.

- The ability to have targeted delivery appears to be a salient risk and opportunity. The application supports the delivery capability with animal studies and improved pharmacokinetics.

- The proposed therapeutic is designed to target the kidney collecting duct cells and knockdown expression of TMEM16a and MCP1.The collecting duct targeted therapy shows ability to substantially reduce cyst and kidney size in model systems and improves renal function in the mouse model. While the data are impressive, neither of the models used can definitively predict success in humans.

- RNA interference is an attractive option for silencing the TMEM16a and MCP1 genes, and siRNA is already deployed in the clinic. Overall, the nonclinical data indicate POC for the therapy and nonclinical therapeutic target in appropriate in human in vitro and animal models designed to recapitulate ADPKD.

- The data in a mouse model indicates that the therapy is not only targeted to the kidney, but also significantly to the liver. This could be a potential concern when administered to human subjects. Severe liver disease is an exclusion criterion in proposed clinical trial.

- Some of the therapies targets are expressed in the lung and other tissues.

- MCP1 is a risky target.

- A reviewer believes the application would be much stronger if only TMEM16a was targeted. The authors showed convincing data in vivo showing POC for using peptide micelle nanoparticles as a vehicle.

- While authors present some evidence in support of this approach, there are key pieces missing and significant concerns about the targets themselves that dampened enthusiasm for the application.

Project Plan and Design

- There is a well developed, clearly described project plan. Clinical planning and regulatory activities are also clearly delineated. The PDEV objective will likely be achieved within specified time and budget. Access and

affordability are well addressed.

- Potential project risks and corresponding mitigation strategies are only briefly described. These include potential renal and liver toxicity in human subjects and manufacturing variability affecting particle size or siRNA loading. The mitigation strategies listed should adequately address these concerns, but such strategies cannot exclude unexpected results with respect to safety in humans. Careful monitoring during the actual clinical trial will be critical.
- While there are significant challenges, the outline of the project plan appears rational in order to achieve the potential goals.
- More mechanistic studies are needed.
- The plan is structured to de-risk translation to an active IND both in terms of manufacturing and preclinical activities.
- The authors verbiage alternates between siRNA “encapsulation” and “covalent linkage” to nanoparticles. This CMC narrative should be clear, as the wording choice drives analytics, potency assays, metabolism, and safety expectations.
- Clinical planning is stage-appropriate. Budget and timelines appear plausible, if manufacturing and GLP tox proceed without major setbacks, and the risk and contingency section anticipates typical bottlenecks and outlines concrete mitigations.
- The three-year project timeline proposed seems aggressive considering the planned manufacturing scale up and nonclinical testing plans, as well as plans to implement the regulatory strategy to achieve IND submission.
- The program is robust but contingent upon scale up of the clinical product for the pivotal toxicology studies and the phase 1 clinical study. Should this fail, the timeline to IND would likely not be met in 36 months.
- The company intends to outsource some of the nonclinical work to a CRO; it is not entirely clear which studies would be conducted there or their timeline to completion. There is mention of toxicology studies in two species; however, the details of these studies or exactly which species will be tested is unclear. One preclinical model takes longer to source, plan and develop bioassays, and conduct the toxicokinetic work that need to be completed than allocated. Thus, meeting the timelines within a three-year window from funding to IND filing is a concern.
- The overall cost of the project to phase 1 is $13 million; cost to CIRM would be approximately $10.8 million. A significant proportion is for salaries with two senior positions (including the CEO) 100% funded. There is also approximately $1.5 million allocated towards clinical activities including clinical start up costs and patient recruitment that could be considered for funding after reaching a successful IND.

Project Team and Resources

- There is a strong leadership team with impressive experience in relevant operations and a stellar advisory board addressing all aspects of the proposed project. Key members of the advisory board provide significant experience in clinical trials including of oligonucleotide therapeutics.
- The plan for coordination and execution of the project is well described and appropriate. CROs have been selected for siRNA synthesis, formulation and for pharmacology and biodistribution studies. Other resources appear appropriate; the involvement of the selected partner institutions for community outreach engagement and trial subject recruitment is a strength of the application.
- The PI appears to have the requisite experience and is committing 100% effort to the project.
- The CEO over allocation and lack of experience in running an actual biotech is a concern.
- The team has appropriate expertise in nanomedicine, RNA therapeutics, and nephrology expertise with

operational leadership. The PI and advisors include experienced clinicians and translational scientists in ADPKD and RNA drug development, which is important for model selection, endpoint strategy, and clinical protocol refinement. On the development side, the choice of CDMO leverages deep experience in oligo and lipid-based formulations, and the selected CRO has capabilities across GLP/Non-GLP pharmacology, toxicology, and bioanalytics. Access to university cores, accredited vivaria, and imaging resources is adequate for the proposed preclinical work, and the Alpha Clinic network is a strength for eventual trial start-up, recruitment, and diversity goals.

- The team appears to have the appropriate level of expertise to meet the goals. The CEO will be engaged 100% to oversee timelines are met. But the CEO also oversees a staff of 250 people, making it unclear how this will be feasible.

- The project plan seems aggressive within the three-year funding window. Should CGMP fail, for example, it is unlikely the timeline will be met. All of the early PDEV and late PDEV activities required to get to an IND have been outlined in the proposal, but there is no Gantt chart that offers a contingency plan should any of the milestones not be met.

- cGMP and manufacturing facilities have been identified and letters of support have been provided with respect to their capabilities. A nonclinical CRO has been identified and a nonclinical study plan is in place (except for species identification) From a regulatory standpoint, a regulatory consulting company has been identified that will assist with IND filing.

Population Impact

- The proposed therapy has the potential to improve outcomes in all affected populations regardless of socioeconomic status. The intended clinical study population is carefully described and appears appropriate given the prevalence of ADPKD in the respective segments of the California population. The age range chosen is optimal for minimizing adverse effects and maximizing therapeutic benefit. Community engagement and Alpha Clinic activities will inform protocol design, patient referral, and trial enrollment strategies. There is a well detailed plan for bidirectional educational sessions with patient advocacy groups such as the PKD Foundation.

- ADPKD disease burden is higher in populations with limited access to nephrology care, where delayed diagnosis may lead to earlier onset of ESRD. In California, certain underserved and rural populations face geographic barriers to specialty care, exacerbating outcomes. The proposed therapy has the potential to benefit all genetically confirmed ADPKD patients, regardless of demographic background,

- IV infusion can be burdensome for patients, limit adoption, and, therefore, the ability to show durability of therapeutic effect over a long period of time. Minimizing dosing to two-three times per year would be very important if subcutaneous dosing is not deemed appropriate.

- The program's attention to affordability—via scalable synthetic manufacturing and planning for payer engagement—supports downstream access.

- The proposal addresses disparities and adoption by incorporating the CIRM Alpha Clinic infrastructure, community engagement studios, bilingual materials, and navigator support to improve trial participation across demographics. Continued attention to diagnostic access, including genetic testing and imaging pathways, will be important to avoid selection bias and to generalize benefits. If the therapy proves safe for chronic use, the potential population impact is high, but it depends on demonstrating durable benefit with manageable monitoring requirements and on ensuring that pricing aligns with long-term, widespread use in a disease that may require treatment over decades.

- The applicants are aware of socio-economic factors that have limited patient access to doctor care and the diagnosis and treatment of ADPKD. With streamlined CMC processes and no need for long-term hospitalization, the projected cost is expected to be significantly lower than biologics requiring complex handling or genetic engineering, making it more accessible to patients and payers. The applicants acknowledge that in California, certain underserved and rural populations face geographic barriers to specialty care, exacerbating outcomes. The proposed therapy has the potential to benefit all genetically confirmed ADPKD patients, regardless of demographic background by providing a targeted, non-invasive

treatment option that does not require complex surgical intervention or hospitalization.

Application #	PDEV-19165
Title (as written by the applicant)	Novel muscle-tropic AAV and RNA targeting strategy for safe and efficacious gene therapy for Duchenne Muscular Dystrophy
Therapeutic Candidate (as written by the applicant)	The therapeutic candidate is an AAV delivered anti-sense oligonucleotide therapy.
Indication (as written by the applicant)	Duchenne muscular dystrophy
Unmet Medical Need (as written by the applicant)	Duchenne muscular dystrophy is a progressive, life threatening muscle wasting disorder for which no cure exists. Existing treatments show low efficacy, and high lifetime costs for patients. The candidate is poised to revolutionize genetic therapies for DMD via higher potency and better muscle delivery.
Major Proposed Activities (as written by the applicant)	• CMC process development and GMP lot production • IND-enabling in vivo studies • Regulatory submissions and IND clearance.
Statement of Benefit to California (as written by the applicant)	Duchenne muscular dystrophy is a genetic disease afflicting >1000 children in California. Furthermore, California (due to its robust medical infrastructure) is a hub of treatment for DMD. While some treatment options for DMD exist, they have shown low clinical efficacy, high costs, and substantial safety risks. Our DMD therapy is designed to deliver optimized genetic cargo more efficiently to muscle cells, improving both potency and safety for DMD patients.
Funds Requested	$12,710,543
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	6
Highest	90
Lowest	70
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	1
(1-84): Not recommended for funding	12

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel’s discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

Key Strengths and Weaknesses

- Safety risk is too high for the mechanism of action.
- Strengths lie in use of a muscle targeting AAV and the precedent set in use of ASO; key concerns associated with targeting muscle based on Sarepta product with dose/cost, durability, and safety; unsure if this will improve upon current standards.
- Novel approach with a new AAV is good, but the application needs more data on manufacturability and vector genomes/diploid genome (vg/dg) in large animal models. Pharmacodynamics (skipping/dystrophin) at lower doses than have been tested are requested (*in vivo* studies equate to north of 1e14, and with the novel capsid, one should be able to reduce this a log or two).
- The project is in the discovery phase. The AAV vector appears to be more muscle tropic, but the assessment is done with pooled libraries in large animal models. Since different AAVs can compete for binding sites, single capsid studies are important.
- Two key issues:
    - It is unclear if the vector gets to satellite cells. Dystrophin is important in these cells, likely for asymmetric division to maintain the pluripotent cell while also contributing to muscle repair. In the context of muscle cell division, which is enhanced with muscle turnover in DMD, the durability of effect is unclear. It may be 2-3 years, but unlike with AAV in post-mitotic tissue, the impact of AAV in mitotic tissue is likely to be substantially shorter.
    - Luciferase expression is not an adequate representation of capsid tropism. Vg/dg levels will better represent tropism of the vector and mRNA levels will better represent productive genomes in single capsid studies. What is really needed are vg/dg to understand if enough payload is getting to the right cells.
- The mouse study used 5E12 vgs/animal. For a 20g mouse, this dose is equivalent to 2.5E14 vg/kg. A rationale is not presented for using doses of 1E12-1E14 vg/kg in the subsequent mouse studies, large animal model studies and in the clinic.
- U7 snRNA approach is previously validated in animal models and in the clinic, so that's appropriate.
- CMC - Productivity of this muscle tropic AAV vs AAV9 was assessed in adherent cultures, and that's not appropriate. The productivity and yield should be characterized in the process that would be used for the clinical supply.
- Applicants are only using corticosteroids for AAV delivery. This is risky, especially at high doses, and many AAV companies are doing triple immunosuppression in patients.
- Overall decent approach, but there's risk related to the capsid's tropism translating to large animal models in single capsid studies, and there's CMC productivity risk.
- Overall, the project is at an early stage and mouse functional studies, off-target assessment, GLP-tox studies, large animal model pharmacology etc. need to be assessed.

Value Proposition

- High unmet need for new therapies; existing therapies have overall fairly low efficacy with significant safety concerns and high cost.
- Borderline value proposition if safety concerns arise at high doses.
- Sound approach as the use of therapeutic antisense oligonucleotides (oligos) is well established. Justification for use of AAV in approach versus oligos, outside of repeat oligo dosing. If repeat dosing is

required is the key question.

- Potential to be cheaper if dose is reduced due to muscle targeting AAV; uncertain about uptake versus approved therapy.
- Exon skipping is good idea, but AAV delivers to a subset of muscle, and with mitotic tissue and uncertain delivery to satellite cells, there's worry that this would be provide only a transient benefit.

Rationale

- Interesting approach, and a lot of data is presented to support the proposed therapeutic approach.
- Novel AAV has serious toxicity concerns.
- Sound approach. However, novel AAVs require more development, which is accounted for in the plan. Unsure if delivering an oligo is best approach (as an investment). Systemic delivery is most concerning due to cost and safety risks. Solid foundation is provided for efficacy of the oligonucleotides.
- The mitotic aspect of DMD muscle is a concern. This approach may only impact patients for 1-3 years, which is what Sarepta has seen in their gene therapy (albeit with microdystrophin, which is very different than the applicant's candidate).

Project Plan and Design

- Well thought out plan provides confidence in the applicant's experience.
- Very good.
- Project appears premature for CIRM support. It appears well-thought out, with promising preliminary research from which to draw, it's just very early (applicant is ~ one year from an INTERACT meeting). It's challenging to assess this based on the stage of development.
- Given how early program is, there's an unclear value proposition for CIRM. Just about every aspect of development is still to be determined.
- Recommend reapplying after conduct of additional early pilot studies.
- Manufacturing concerns for scale up. Poor manufacturing could lead to serious adverse events.

Project Team and Resources

- Great team.
- Appears to be a good team with the necessary expertise.
- Sound CDMO selected, however this reviewer could not find much information about one vendor and its associated personnel. The plan suggests expertise exists, but the reader cannot confirm it. Well thought out plan, but little information could be found on the depth of gene therapy experience with team (outside of the CDMO).

Population Impact

- High potential for impact.
- 1600 patients in the US with exon 51 DMD.
- Adequate impact if it works.

- Applicable to subset of DMD patients, creating complications with adoption vs available approved product. Uncertain the AAV oligo approach is best. This panelist generally doesn't favor DMD as target due to systemic delivery and the potential for poor durability.

Application #	PDEV-19135
Title (as written by the applicant)	A Novel Vasculogenic Stem Cell Product for the Treatment of Critical Limb Threatening Ischemia (CTLI)
Therapeutic Candidate (as written by the applicant)	The therapeutic candidate is an 'off-the-shelf' iPSC-derived vasculoprogenitor cell (iVPC) that initiates vasculogenesis in ischemic tissue.
Indication (as written by the applicant)	This therapy is for critical limb threatening ischemia (CTLI) patients with rest pain, reduced mobility or ineligible for traditional revascularization.
Unmet Medical Need (as written by the applicant)	For ~30% of CLTI patients, revascularization fails, leaving amputation as the only option, with ~ 50% 2-year mortality rate. Current palliative therapies don't address the root cause or rebuild vessels. Our regenerative iVPC therapy aims to restore blood flow to prevent limb loss and save lives.
Major Proposed Activities (as written by the applicant)	• Transfer cGMP biomanufacturing and testing process, generate batches of clinical-grade iVPCs and perform stability studies. • Conduct IND-enabling safety, biodistribution and toxicology preclinical studies in clinically relevant models to demonstrate the product's safety. • Prepare and submit a comprehensive IND application to the FDA for IND clearance, enabling the launch of a first-in-human clinical trial in California.
Statement of Benefit to California (as written by the applicant)	Chronic Limb Ischemia impacts thousands of Californians, leading to devastating and costly amputations often paid by public funds. This project, a CA-based partnership, develops a scalable, off-the-shelf regenerative iPSC-derived vascular progenitor cell (iVPC) therapy to restore blood flow, prevent limb loss, and significantly reduce the economic burden (>$500K/patient) of this disease. This directly benefits the health of our citizens and the state's economy, fulfilling CIRM's core mission.
Funds Requested	$7,499,998
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	78
Median	80
Standard Deviation	6
Highest	85
Lowest	60
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	1
(1-84): Not recommended for funding	13

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to

indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

Key Strengths and Weaknesses

- This off-the-shelf product is well advanced in terms of CMC, although there's still some work to do.
- No mechanism or rationale suggests these cells are better than other cell therapy products tested in chronic limb ischemia (CLI). The effect is transient and likely to be paracrine.
- Pre-clinical data are not compelling as compared to other agents that have tread the same path. The target clinical indication is good. The mechanism is not clear from the data.
- Strong CMC package.
- Weak mechanism of action for durable effects.
- Key Strengths: Off-the-shelf manufacturing; the goal to drive towards vasculogenesis over angiogenesis; potential for reduced immunogenicity; single clinical site approach simplifies execution.
- Key weaknesses: Durability and questionable cell persistence to drive repair in animal models; CMC efforts are potentially too extensive to be ready for clinical product manufacturing; project plan does not address plans for scalability to multiple clinical sites.
- The mechanism of action requires further investigation.
- Strong manufacturing plan with high likelihood for commercial success.
- Strengths: Excellent team; plan developed according to FDA pre-IND meeting in 2021.
- Weaknesses: Mode of action unclear; no benchmarking against similar approaches; no proof of vasculogenesis; no proof of low immunogenicity of endothelial cells derived from iVPCs in vivo.

Value Proposition

- The unmet medical needs and health care costs of peripheral arterial disease alone are huge and this could have great impact. If successful, this treatment would be much more accessible than other treatments in process. The plan presented appears to be very practical especially because of the partnership involved.
- Potentially meaningful and substantial improvements in clinical outcomes are suggested by the in vitro data and in vivo animal data.
- The expected impact of addressing this medical need is to preserve patient function, capability and health. Caregivers burden and costs will be lower/reduced because of improved patient health. Similarly, the healthcare system would expend less overall, with patients staying out of hospitals and being more easily supported in home healthcare.
- Not a compelling value proposition. The applicant did not sufficiently differentiate the proposed product from other similar products that have failed. Based on proof of concept data, there's a low likelihood of this being a transformational therapy. While promising, it does not meet threshold for CIRM funding.
- Durable effects likely require higher cell integration than demonstrated in the proposal.
- Accessibility and affordability would be dependent on the off-the-shelf nature (a positive) and scalability (an unknown) of making iVPCs from a banked iPSC line that can be delivered to patients. A cryopreserved drug product (DP) will require sound logistics to reach all patients who need it. There do not appear to be potentially competitive, off-the-shelf allogeneic products FDA-approved in the US.

- The feasibility and practicality of uptake compared to standard of care will vary in timing by stakeholder – patients and caregivers are looking for solutions where the patient retains independence by retention of tissue/limbs, has low or no pain associated with their vascular loss, and is accessible. Therefore, these populations are likely to be accepting of the route of administration and clinical follow-up needed to assess the treatment. The healthcare system will follow if the clinical data support reduction in healthcare costs based on above factors as well as durability.

- Peripheral arterial disease and critical limb ischemia are an unmet medical need with significant health consequences.

- iVPC therapy promises to restore vasculature as curative approach versus symptom-management or mechanical interventions currently as standard of care.

- Strong pre-clinical animal data demonstrating functional improvement.

- Cost-comparability of the current process with standard of care including a cost of goods reduction through further optimization of commercial manufacturing is a strength. Removal of iPSC gene-editing removes the high cost of CRISPR licensing.

- Allogeneic off-the-shelf product streamlines manufacturing, distribution, and patient delivery.

- Chronic limb ischemia (CLI) is clearly an unmet medical need. It is difficult to assess the applicant's approach to efficacy without benchmarking studies. However, current cell therapies in clinical trials include MSC and peripheral blood-endothelial progenitor cells (EPCs being the equivalent in vivo cell type for iVPCs). Preclinically, between MSCs and EPCs, there is little efficacy advantage of one over the other (PMID: 396121222, 33436054). Additionally, the combination of MSCs and EPCs displays the highest efficacy impact (PMID: 39004727). The applicants claim that iVPCs are an improvement over MSCs as MSCs act transiently and via a paracrine effect. However, the data presented from the applicants also show a transient effect of iVPCs, suggesting a paracrine mechanism. In fact, as shone in the applicants' in vivo study, the iVPCs and/or derived cells are cleared in less than a month. Clear comparative studies as well as benchmarking would be helpful to clarify the benefit over existing cell therapies in trials.

- The benefit of the applicants' approach is product consistency; this has been a challenge for MSC-derived therapy. However, cost and scalability of MSCs is theoretically better.

- Key questions: (1) Immunogenicity; a requirement for immunosuppression may reduce willingness of patients to accept treatment) (2) Retention: vasculogenesis is unlikely to be sustainable; preclinical evidence suggests loss of cells in less than a month (3) Mode of action: it's unclear whether these cells' effects truly differ from alternative cell implant approaches that have shown little clinical impact.

- Advantage: allograft, off-the-shelf potential, scalable iPSC-technology, economy of scale.

Rationale

- Scientific rationale to promote vasculogenesis as a repair and restoration method makes sense. It's unclear whether cryopreserved drug product (DP) was used for the proof of concept animal studies; however, this will be tested in the proposed nonclinical activities. If fresh DP was used in previous animal studies, outcomes may differ when compared to outcomes using the thawed, diluted DP that will be used for the planned preclinical studies.

- Animal efficacy data are based on the preferred mouse model (BALB/c nude mice) and use contrast imaging. Establishment of an in-house hind limb ischemia model at the applicant institution is advantageous to be able to rapidly undertake non-GLP studies for assessing significant manufacturing changes where comparability is needed to assure clinical results can be analyzed collectively.

- Lack of cell persistence and long term durability of effect remain. These are questions to more fully explore, ideally in systems that don't clear iVPCs from tissue due to xenotransplant immune responses.

- Little cellular integration and likely a transient effect.
- Rationale for injecting endothelial precursors into ischemic tissue is sound; they will hone to hypoxic tissue and stimulate angio- and vasculogenesis.
- The unmodified iPSC starting material does not stimulate significant immune response despite presence of HLA I/II.
- iVPCs demonstrate a stable phenotype, high viability, and appropriate endothelial biomarkers.
- Strong in vivo evidence of efficacy in animal models of hind-limb ischemia.
- Strong scientific rationale, biologically relevant study design, and demonstrated preclinical efficacy and safety.
- The robustness of the scientific rationale is strong. Creating or inducing vasculogenesis in the area of injury for chronic limb threatening ischemia could be a potent way to address the unmet need. Until benchmarking or comparative studies are conducted, it is difficult to determine if the approach shows benefit over other therapeutic strategies, such as MSCs.
- The iVPC approach could be strengthened by demonstrating true long-term engraftment of iVPCs. This may require gene editing for hypoimmunity or immunosuppression. The applicants claim that the iVPC display low immunogenicity due to expressing CD47 and not eliciting a T cell response in an MLR assay. Expression of CD47 alone isn't sufficient to demonstrate escape from NK cells. Further, it isn't clear if the MLR assay was conducted with PBMCs from one or two donors. Either way, there is high variability in an MLR reaction requiring multiple donors to test validity. Additionally, while iVPCs may lack immunogenicity, we don't know if this would also hold true for the endothelial cells derived from these progenitors. As shown in one of the preclinical studies, the iVPC and resultant cells are cleared in less than a month, at minimum.
- The applicants utilized a relevant model and demonstrated functional efficacy improvement. However, it isn't clear if the efficacy benefit is above other cell therapy approaches for chronic limb threatening ischemia, as discussed previously.
- The strengths of the data presented are: demonstration of efficacy in a relevant animal model, well characterized manufacturing process and initiated tech transfer, potent iVPC, strong in-vitro and in-vivo data from the collaborating lab and pre-clinical work from the original cell process developer.
- The weaknesses: The mechanism of action isn't understood. It isn't clear if the efficacy is an improvement on current pre-clinical and clinical studies in the field. If the efficacy is driven by paracrine mechanisms, potency assays should reflect that, as opposed measuring to tube formation.
- Significant preclinical work in mouse models of hindlimb ischemia supports the application.
- Low immunogenic potential is assumed, but not confirmed. It is doubtful that iVPCs, especially after endothelial differentiation and maturation, will exhibit a low immunogenic profile, even if expressing CD47.
- Hypoimmune strategies are suggested to mitigate the risk of rejection. It could well be that the inflammatory reaction to immunologically competent cells is important to induce an angiogenic response.
- It's unlikely this approach will lead to cell retention and lasting vasculogenesis, and this is proposed as a unique selling point. The key mode of action is more likely release of pro-angiogenic factors triggering angiogenesis. Proteomic identification of pro-angiogenic factors and comparison of the cells against direct pro-angiogenic factor application would be appropriate.
- Loss of implanted cells is further confirmed by the presented preliminary data; after about three weeks no cells were detected according to the applicants.
- How does this differ from earlier endothelial progenitor, bone marrow mononuclear cells, or mesenchymal stem cell implantation studies in the same target patient population? Is there evidence for a distinct

secretome?

Project Plan and Design

- The plans appeared to be very practical with a very well-thought-out approach to production and financial contingencies. The affordability and the off-the-shelf access make this seem very marketable.
- Good readiness for GMP, but scale up is not well articulated.
- Proposed CMC activities, though simplified by no longer needing a gene-editing step, do not appear to include requiring the removal of reagents that are animal-based/-derived. Implementation of next generation sequencing (NGS) screening of all raw materials that require it is suggested as a first-line raw material release testing strategy. It is encouraged to source suitable, non-animal derived, alternatives and utilize such in manufacturing, without incurring the time and materials expense and possible risk of rejecting key raw materials by NGS prior to making product for clinical use.
- The applicant's commitment to qualify a multi-attribute potency assay for use during Phase 1 is responsive to FDA's pre-IND feedback. The agency has not formally reviewed the approach; therefore, acceptability of the assay for pivotal data DP release testing remains a question until FDA provides their feedback.
- The applicant plans for a single site phase 1 study; therefore, scaling to multiple clinical sites is not being evaluated.
- A GMP manufacturing process is already established with appropriate Master Batch Records, SOPs, and Bill of Materials. Clinical material is already manufactured and released using the current process.
- Consideration is given for feasibility, engineering, and GMP runs.
- It's unclear from the proposal how, and to what degree, scale-up will be achieved (e.g. stirred tank bioreactors vs hyperflasks, etc.).
- The plan implements appropriate mitigation strategies for residual undifferentiated cells and potency.
- Cost modeling is included to support future market access.
- With the addition of determining the mechanism of action and potency assays based on the MOA , the proposed activities are necessary and appropriate to efficiently and effectively progress the project to IND clearance.
- If the applicants determine that the cells are indeed immunogenic, and graft durability is important for improved MOA, they would either need to gene edit the PSCs to render them hypoimmune or utilize immunosuppression.
- The applicants could elaborate more on plans for scale up and cost reduction to access a larger patient population.
- The project plan is well designed and considers advice obtained from FDA pre-IND meeting in 2021.
- At this stage of development, the project is clearly outlined.
- All important aspects of CMC and IND-enabling preclinical work are covered in the plan.
- Appropriate risk mitigation and contingency plans are included.
- The applicants have involved a consultant to determine pricing and reimbursement.
- A hypoimmune strategy is mentioned, but apparently it's not a focus.

Project Team and Resources

- Team leadership is appropriate and has the clinical expertise to execute the animal and initial human studies.
- Strong team.
- The team appears to have access to all the necessary resources and facilities to initiate their proposed clinical study. Transferring the process to the applicant's manufacturing center leverages the center's skills and capabilities to produce early phase clinical product. Similarly, leveraging the applicant's clinical operations infrastructure for a single site study makes sense. The sale of a controlling equity interest in the initial cell developer to the applicant institution and relocating operations there provides several benefits to the developer they would otherwise not have.
- The collective team, including consultants and contractors, appear to have the expertise and experience to take on this project, particularly in light of lessons learned from the pre-IND responses.
- Strong team with proven clinical manufacturing experience.
- Appropriate GMP facility with institutional support.
- The appropriateness of the team is a strength of the application. The manufacturing capabilities of the group are of notable value to the project. They are leaders in the field of manufacturing PSCs and their differentiated cell types. The applicants have secured the appropriate partners, along with letters of support to enable their work. Additionally, they have replicated the murine surgical techniques potentially necessary as a back up strategy.
- Through their work at the host institution, as well as their contracted CROs, the team has access to necessary resources and facilities.
- The applicant and the initial developer of the cell process have expertise in GMP-compliant, scalable production of iPSC lines und vascular endothelial cells.
- The manufacturing center's expertise will ensure and coordinate cGMP iVPC manufacturing for IND filing and phase I/II testing
- Regulatory affairs experts are involved in IND filing for the ultimate phase I/II clinical trial.

Population Impact

- The applicant presents a well thought-out plan for engagement of individuals to match the demographics of the study region.
- The applicant has strong community partners.
- The applicant understands the medical/treatment landscape and recognizes potential hurdles such as price, accessibility and accessing underserved populations.
- The intended clinical study population appears reasonable.
- Co-morbidities as limiting factors, such as diabetes, are considered.
- Demographics are considered.
- Patient perspectives are not incorporated.

Application #	PDEV-19142
Title (as written by the applicant)	Universal hiPSC Skeletal Muscle Cell Therapy for Localized Atrophic Muscles after Chemoradiation in Sarcomas
Therapeutic Candidate (as written by the applicant)	Allogeneic, universal cell therapy for localized muscle atrophy after sarcoma and chemotherapy and/or irradiation
Indication (as written by the applicant)	Sarcoma cancer patient survivors with muscle loss resulting from localized limb sarcoma and preoperative chemotherapy and radiation treatment.
Unmet Medical Need (as written by the applicant)	Treatments for muscle loss after chemo and/or irradiation recovery primarily focus on improving nutrition through increasing caloric intake and nutritional supplements, or exercise. However, there is currently no accepted standard medication for treating muscle atrophy itself.
Major Proposed Activities (as written by the applicant)	• Completion of CMC, safety and efficacy studies for our universal hiPSC SMPC cell therapy • Clinical planning and patient outreach for trial preparation • FDA pre-IND and IND package development
Statement of Benefit to California (as written by the applicant)	Cancer induced muscle wasting is estimated to kill 175,000 Californians each year. In the US, there are 229,000 people with sarcomas, and 18,000 new cases/year. The standard of care for sarcomas is chemotherapy and high doses of radiotherapy, but these cause tissue toxicity in the nearby muscles. We will address an unmet need for cancer survivors through reconstructing skeletal muscle following localized muscle atrophy using a universal therapy that will reduce costs and increase accessibility.
Funds Requested	$12,998,288
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: 78

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	76
Median	78
Standard Deviation	5
Highest	83
Lowest	70
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	13

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel’s discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in

the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

Key Strengths and Weaknesses

- An "off the shelf", hypo-immune cell product is valuable, and the technology has the potential to apply to other diseases. This would be important. The applicant hasn't yet had an INTERACT meeting, and it's difficult to see a clear path to an open IND.
- Too early and risky; the applicant will benefit from an FDA INTERACT meeting.
- There is a high unmet need, and the proposed idea has promise. However manufacturing plans have a high degree of risk, and preclinical planning is not sufficient.
- Strong clinical need. Approach is logical but has high manufacturing needs. There are some limitations in the applicant's present affordability knowledge and the planning regarding the preclinical package and manufacturing path.
- Only a single figure appeared to show true disease-modifying activity, though the model used was impressive. However, it was not clear why so much effort was made to develop the mouse model and then propose use of other models for all of the included milestones.
- Since an INTERACT is planned for fall of 2025, it would be better for the applicant to meet with FDA to straighten out exactly which animal models are appropriate for driving this program to a successful IND.
- The applicants have developed a differentiation protocol that works in multiple pluripotent cell lines and produces skeletal muscle progenitor cells (SMPCs) that can differentiate into mature muscle cells in various animal models. The fact that they have developed this protocol and that it works efficiently in multiple pluripotent cell lines is a strength.
- The applicants plan to use a universal pluripotent stem cell line that can be used in an allogeneic setting. It has been engineered to evade immune detection. While this approach is appreciated, this cell line has not been approved by FDA for use in human subjects. That is a weakness; we don't currently know what safety studies FDA will require to use the cell line in humans. The cell line does include a "kill switch" that has been tested in vivo. That is a positive, but it doesn't elucidate the tests FDA will require before human use is approved.
- The applicants also plan on using an automated system from for growth and differentiation of cells. While the automation idea is attractive, the reviewer isn't aware that this system has been used in any manufacturing processes that currently have FDA approval for clinical use, and therefore, they would not recommend trying this approach for a first in human (FIH) clinical trial.
- The applicants have had no interactions with FDA, and there will be challenges completing this project in a timely manner and on budget. While the use of a universal cell line and automation of the manufacturing process are desirable, in the long run the applicants have underestimated the complexity of incorporating all these things into a FIH clinical trial.
- Positive feedback from FDA and a clear roadmap to complete the work necessary to file an IND and proceed to the clinic would increase support for the project.
- Strengths: team and preclinical work.
- Weaknesses: residual immunogenicity; lack of biomarkers for cell retention; small effect sizes described as base and optimal cases; no FDA feedback.
- The rationale related to the potential impact was difficult to interpret in terms of value proposition. It was not clear from the application how meaningful the product would be even if it met its target product profile "best case" efficacy scenario of only small percentage increases in strength and muscle mass.

Value Proposition

- Reconstituting skeletal muscle with SMPC in patients with localized muscle atrophy following sarcoma treatment is a novel and exciting strategy, and it may offer a desirable outcome in affected patients.
- The proposed off-the-shelf iPSC-derived allograft approach appears scalable and affordable, at an assumed cost of goods is approximately $60K, considering the disease condition associated standard of care costs.
- There are currently no treatments for muscle wastage after surgical resection of localized soft tissue sarcomas and subsequent radiation and optionally, chemotherapy. To that extent, this approach offers hope for regeneration of new muscle in these patients.
- The approach for inducing allogeneic cell tolerance is appealing.
- Use of hypoimmune, fail-proof cells, derived from an already existing iPSC-source, for a universal application is interesting.
- If effective, this therapy may have impact for other conditions that cause muscle cachexia.
- No current effective treatments exist for radiation-related cachexia in sarcoma.
- Plans to ensure accessibility and address issues of affordability are included throughout the proposal. This is one of the most detailed and robust plans the panelist has seen in the PDEV applications they reviewed, and that's a major strength from the patient advocate perspective.
- The applicants have generated a directed differentiation protocol that generates skeletal muscle progenitor cells (SMPC) that are further purified using cell surface markers. This differentiation protocol has been demonstrated in multiple cell lines including an iPSC line that has been engineered to evade the human immune system. In addition, this cell line has a "kill switch" incorporated should there be any off target cell growth that may cause safety concerns.
- SMPC have been transplanted into immunocompromised animal models and show survival and differentiation into mature skeletal muscle cells.
- This is an early stage project that will involve adaptation of the differentiation and sorting protocol to a GMP cell line, manufacturing in a GMP facility and subsequent testing of the differentiated cells in animal models leading to an IND filing.
- The applicants have not had any meetings with FDA to seek feedback on their proposal.
- The approach, intramuscular injection will be feasible. Questions relate to: (1) the actual defect size and condition (acute, subacute, chronic) which may be realistically targeted, (2) durability of the anticipated effect, (3) immunogenicity, despite the elegant hypoimmune approach, and (4) clinical monitoring of graft retention via blood derived biomarkers.

Rationale

- The applicants have demonstrated that cells can engraft and differentiate in various immune compromised animal models; the rationale is sound.
- The differentiation protocol has been tested in various cell lines (including a research grade immune evasive cell line) and appears robust, so issues issues adapting the protocol to the GMP cell line aren't anticipated.
- The applicants can refer to a large body of literature with convincing and exciting muscle reconstitution data in radiation damaged mouse models from the applicants' lab.
- The use of a "universal" iPSC to generate SMPC that can be used in an allogeneic setting is attractive. The ability to treat patients in a timely manner and to manufacture large lots to treat multiple patients will

decrease costs compared to autologous approaches.

- Off the shelf accelerates the pace of accessibility vs an autologous approach.
- Rationale is fair. The applicant had a very good disease model, but is not really focusing on it.
- The first two disease modifying studies are questionable in terms of whether there is disease-modifying activity.
- The injection delivery modality is associated with some patient burden; it's unclear if this therapy may eventually be available through an at-home delivery system for IM injections.
- The proposed 70% SMPC purity as base case scenario appears quite low. How do the applicants control the remaining 30% of cells, and can sufficient safety data can be obtained to exclude iPSC-derived teratoma or sarcoma formation? This will be answered in the proposed study, first in mouse and then in large animal models (contracted to a CRO).
- The applicants intend to use rodents with a "humanized" immune system to test universal donor cells. These animal models are no substitute for an actual human, so the ability to evade the human immune system will only really be known once the product is tested in humans.

Project Plan and Design

- Project is well designed with comprehensive early and late product development with a focus on purification, automation, reproducibility (testing in several iPSC-models), and studies in animal models. The clinical study plan is sound with a primary focus on safety and tolerability (for which the immunosuppression requirement remains to be clarified). Tumorigenicity assessment over 12 months is adequate, but could be extended by long-term off-study study registry data.
- Exclusion criteria are thoughtful and included important comorbidities that are sometimes missed in phase 1/2 studies (e.g., psychiatric and substance use).
- Patient reported outcomes are measured at each follow-up time point.
- The project is not focused towards obtaining an active IND. Too many models are proposed, and the applicant needs a clear, focused plan on how to progress to IND based on an INTERACT meeting. How meaningful is a 1-2% change in muscle mass? Is it for a specific group of muscles or total body muscle mass? The manufacturing path is unclear due to the use of new technologies; this introduces risk.
- There is some confusion why additional models are being developed in a second rodent species.
- There are late PDEV activities to do large animal studies that may not be needed. The application justified this solely on a paper associated that used the model from another group. While the this paper is noted, citing it as evidence of FDA requirements is a stretch. Better justification for the use of the model is needed in the application.
- The applicants intend to use a robotics approach to manufacture cells. While a reviewer supports the future use of automation to grow and differentiate cells, they discourage the use of this technology at this early stage of development.
- The objective should be to get the product into the clinic as expediently as possible, and this automated technology is not the most straightforward way to proceed. This opinion would change if FDA had a history of dealing with this manufacturing platform.
- A cell therapy company has completed a deal with the automated cell process device manufacturer, but the cell therapy company in question is already in the clinic with their autologous product. Thus, they are in a completely different position in terms of product development.
- The applicants are at a very early stage of development without any regulatory feedback to guide them.

There is significant risk that the timeline and budget will not be achieved.

- The cell dose seems low. Likely only a fraction of the implanted SMPCs will reconstitute the satellite cell niche. Preclinical and ultimate clinical data will clarify feasibility.

Project Team and Resources

- The team and resources are appropriate for the proposed project.
- The team is very experienced in the relevant basic science.
- The university site selected to manufacture cells is well versed in the manufacture of both allogeneic and autologous cells under relevant GMP conditions for clinical trials.
- Excellent team consists of muscle stem cell experts, a pioneer in hypoimmune technologies, and clinical experts on sarcoma treatment in internationally leading centers.
- Pivotal animal studies are contracted to a CRO with expertise in preclinical testing of gene and cell therapies.
- This PDEV application follows two DISC awards and is supported by a team member with successful experience in IND filing for an iPSC-derived cell product.
- There is slight concern that a previous CIRM award that closed indicating progress was only made on 2 of 6 milestones. That said, the applicant appears to have changed approach in terms of the starting cell line.
- That the project is very early stage with no regulatory feedback is a concern. The combination of the applicants plan to use a cell line that evades the immune system and manufacturing procedures that have not been evaluated by FDA or any other regulatory body induces worry that the project will experience significant delays.

Population Impact

- Accessibility and affordability are considered throughout.
- The application appears to be strongly focused on their patient population, and has provided a thorough background on available treatment options, patient needs, and financial impacts.
- The applicants plan to target diverse populations which include non-English speaking and rural communities.
- Their educational materials will be provided in multiple languages.
- The recruitment strategy is expected to reflect the demographics of two diverse California counties near the host institution.
- Patient perspectives are incorporated, with a strong expression of interest in the proposed SMPC therapy.
- Speculations on a broader application in cachexia are a bit farfetched.
- The potential requirement of immunosuppression despite the proposed use of a hypoimmune approach will need to be considered. A benefit-risk assessment in the context of patient perspectives would be helpful.

Application #	PDEV-19161
Title (as written by the applicant)	A Novel Non-viral DNA Gene Therapy for Hypophosphatasia
Therapeutic Candidate (as written by the applicant)	A novel double-stranded circular DNA construct encoding the tissue non-specific alkaline phosphatase protein (TNALP)
Indication (as written by the applicant)	Hypophosphatasia (HPP)
Unmet Medical Need (as written by the applicant)	Compared to the current standard of care, STRENSIQ, this product enables more sustained and physiologically appropriate enzyme replacement therapy with significant reduced treatment burden, broader patient coverage including adults with milder phenotype, and improved affordability and access.
Major Proposed Activities (as written by the applicant)	• Optimization and large-scale manufacture of the Drug Product to support the proposed nonclinical studies • Completion of IND-enabling studies to support safety, efficacy and tolerability of the Drug Product • Preparation and conduct of an IND meeting with the FDA
Statement of Benefit to California (as written by the applicant)	The proposed research addresses a major unmet medical need by developing a more patient-friendly and accessible treatment for Californians with all forms of HPP. By potentially improving patient outcomes and reducing the burden on the healthcare system, it directly benefits California's population. The project also supports non-viral in vivo gene therapy innovation, strengthening the state's leadership in advanced therapeutic development.
Funds Requested	$12,670,039
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: 75

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	73
Median	75
Standard Deviation	7
Highest	85
Lowest	60
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	2
(1-84): Not recommended for funding	11

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in

the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

Key Strengths and Weaknesses

- Possibility to validate a novel non viral genetic modality with the potential for repeat dosing.
- Key strength is novel treatment would address an unmet need in this rare genetic disease. Currently approved treatment is very expensive and requires frequent redosing.
- Key weakness is efficacy of novel treatment is shown only in mouse knockout model and not yet shown in a larger animal model. Also still unclear how durable this treatment would be.
- Value proposition is not clear.
- Value proposition is low; preclinical data suggests waning over time.
- CMC section is weak on details of how this product candidate is to be developed to reach patients.

Value Proposition

- The value proposition is for a less burdensome, potentially safer and potentially more cost effective option to treat people with hypophosphatasia (HPP)
- Value proposition seems reasonable at a high level.
- Very rare condition - Unclear value vs. standard of care and next generation enzyme replacement.
- Rare indication with available standard of care and next-gen therapies in Phase 3 trials - low value proposition of a novel modality.
- There is great potential for the proposed therapy to substantially improve outcomes for the intended population: subjects with the rare genetic disease hypophosphatasia. Currently, there is one FDA-approved (2015) treatment - asfotase alpha. Problems with this treatment include: indicated only for severely-affected subjects, side effects and development of neutralizing antibodies limiting efficacy, need for frequent and indefinite dosing, tremendous cost ($750k-2 million/yr/patient).
- Proposed therapy has potential to allow treatment of many more subjects with HPP including those with mild forms, major cost reduction (although exact pricing yet to be determined), much more convenient dosing schedule, greater efficacy and reduced side effects. For all of these reasons, the proposed treatment has excellent prospects for uptake by patients, caregivers and the overall healthcare system.

Rationale

- The rationale for gene mediated enzyme replacement via systemic delivery is supported by current protein enzyme replacement strategies.
- The scientific rationale for the proposal is strong. Enzyme replacement as currently practiced with infusions of the enzyme protein has already been shown to ameliorate HPP manifestations.
- The proposed treatment with a proprietary circular double strand DNA encoding the enzyme (Fig. 1) should lead to secretion of therapeutically effective levels of enzyme from the liver targeted via lipid nanoparticles. The proposed route of administration is parenteral (subcutaneous or intravenous). Supporting data are strong and include evidence for enzyme secretion into plasma of Alkaline Phosphatase (AP) knockout mice modeling the disease. Figs. 2-4 show rise in AP in plasma of mice injected with the construct, as well as improved survival and bone length. Limitations of the data presented are that effectiveness of the therapy in mouse models may not accurately predict effectiveness in human subjects. The applicant indicates need for further study in large animal models, including large animals.

- Preclinical data not sufficiently convincing of durable and meaningful impact.
- Proposal contains little information to justify the therapeutic approach.

Project Plan and Design

- The application describes a series of activities that appear appropriate to advance the project to IND clearance. These include optimizing the construct and lipid nanoparticle delivery vehicle; further evaluating efficacy in mouse model; contracting with CRO for manufacture and for large animal testing; safety, efficacy and tolerability testing; development of phase 1/2 clinical trial protocol.
- The project objective should be achieved within the 36 months proposed. Significant risks to successful project completion are recognized in the application, and mitigating/contingency plans addressing these are listed. There is a good commercialization strategy that addresses affordability and future market access.
- Very limited preclinical proof of concept data is provided with a prototype construct. Durability and potential for immunogenicity are currently not clear but and are key parameters to ensure successful translation and ultimate clinical development.
- Significant work is planned to develop and optimize a lead candidate including the proposed delivery system.
- Justification for animal model including age of therapeutic intervention will be needed. It is expected that toxicology studies may be needed in large animals to optimally assess not only PK/biodistribution and immunogenicity but also safety. Safety pharmacology endpoints can be incorporated into this study.
- Since selection of a lead candidate will be a lengthy process it may be more efficient to forgo the INTERACT meeting.
- It is difficult to evaluate efficiency when no assumptions are provided about how much drug substance and drug product are needed to supply estimated project needs for clinical and nonclinical studies, process and analytical development studies, stability studies, and clinical in use stability studies. Applicants appear to rely on CDMOs to develop processes and make supplies under GMP with appropriate controls.
- Applicants do not appear to have had contact with FDA about a pre-IND discussion.

Project Team and Resources

- There is a strong team with relevant leadership and expertise. The staffing plan is well described. The plan outlined for coordination and execution is excellent. Necessary resources and facilities appear to be appropriate.
- The corporate team appears experienced in drug development but may be stretched as two proposals have been submitted for consideration.
- It is unclear on the extent to which the collective team has a demonstrated track record in gene therapy projects. The application alludes to other projects underway using the vector but the details are unclear.
- Proposed manufacturing is well planned but at a very early stage.
- Applicants' seem to have experience in proposed areas of effort. CDMOs identified seem to have relevant experience doing proposed activities. However, the level of detail provided in the proposal does not allow for a clear understanding of the practicality of the proposed project plan, or to judge the resources required to implement it.

Population Impact

- An access and affordability plan is considered for the intended patient population.

- The application describes in some detail the composition of the population identified as having the genetic defect leading to HPP. In this regard, the intended clinical study population appears to be appropriate. For example, severe liver disease is an exclusion criterion for study enrollment given that the vector is targeted to the liver to enable synthesis there of the enzyme protein and secretion into plasma.

- The initial proposed study population is subjects with HPP age >5 years and meeting FDA criteria for enzyme replacement therapy. If targets are achieved in initial phase, study population would eventually be extended to all subjects with HPP, including milder forms.

- The applicant has consulted with a patient advocacy group and incorporates their input throughout the proposed project.

- Very low population impact.

Application #	PDEV-19148
Title (as written by the applicant)	Autologous MPO Knock-Out Hematopoietic Stem/Progenitor Cells for Pulmonary Arterial Hypertension in Systemic Sclerosis
Therapeutic Candidate (as written by the applicant)	Autologous MPO Knock-Out Hematopoietic Stem/Progenitor Cells (HSPC) for Pulmonary Arterial Hypertension Associated with Systemic Sclerosis.
Indication (as written by the applicant)	Treatment of pulmonary arterial hypertension (PAH) associated with systemic sclerosis, a severe autoimmune-mediated vascular disease.
Unmet Medical Need (as written by the applicant)	Pulmonary arterial hypertension (PAH) is a rare, progressive, and ultimately fatal disease that may occur as a complication of Systemic Sclerosis (SSc); median survival for patients with SSc-PAH is only 3.0 years. Our stem cell therapy may control the disease and improve the quality of life.
Major Proposed Activities (as written by the applicant)	• Complete pre-clinical pharm/tox studies, including GLP toxicology study, and FDA-recommended genotoxicity studies. • Perform three GMP qualification manufacturing runs of Drug Product meeting all release criteria and initiate DP stability study. • Finalize clinical protocol and associated trial documents, obtain preliminary review by IRB, IBC, and DSMB, and compile and submit IND.
Statement of Benefit to California (as written by the applicant)	Pulmonary Arterial Hypertension (PAH) is a progressive condition for which there is no cure. We are developing a treatment for PAH by transplanting autologous HSC with MPO gene knock-out. The goal is to advance this novel therapy to clinical trials for PAH associated with Scleroderma, an autoimmune disorder often complicated by PAH. California patients with PAH in SSc may directly benefit.
Funds Requested	$7,500,000
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: 70

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	71
Median	70
Standard Deviation	5
Highest	84
Lowest	65
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel’s discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in

the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

Key Strengths and Weaknesses

- Overall concerns relate to (1) the lack of evidence that myeloperoxidase (MPO) is a target in this condition, and (2) even if it is a target, the process of HSCT is associated with poor outcomes in clinical trials. Where there is existing PAH, the edited cell will not affect the pre-conditioning regimen, nor is it likely to acutely reverse PAH. It may, if MPO was a target in this disease, ameliorate it in the much longer term but the risks of the HSCT are over a much more acute phase.

- The proposed therapy offers a potential improvement current standard of care but relevance of MPO to disease has not been clearly shown.

- Value Proposition and Rationale: The major weaknesses are that the models chosen to assess the rationale are not relevant models to this disease and bias the results towards confirming the sponsor's hypothesis that MPO is a key mediator of pathogenesis. Most patients are already MPO-deficient and therefore, MPO is not likely to be a major contributor to disease. So the first major weakness is that there is likely to be no benefit to patients. The second major problem is that the proposed therapy will, in fact, endanger these patients. The reasons that there is no transplant done on Ssc-PAH patients now is due to the risks to these patients. The conditioning regimen would be the same as what is done for transplant and would endanger the patients, causing increases in mortality. So the major weaknesses are lack of benefit and significant risks.

- Favorable based on IND readiness--the animal model was acceptable for the proof of concept study. Toxicity study is do-able and includes off-target effects which would address potential for specificity of the target. The underlying concern relates to the MPO target given that patients present with immune complex-mediated disease.

- Concerns relating to MPO not being a specific target in Pulmonary Arterial Hypertension in Systemic Sclerosis. Require more evidence that the target is accurate; this is not evidenced preclinically, and there's a degree of uncertainty around whether MPO is an actual target for PAH in SSc.

- High risk to patients.

- From a CMC perspective, the package is in good shape. The investigators addressed concerns about the CMC activities.

- CMC concern; a very high level of MPO knock out is required in the cells to get an effect. This is confirmed by the applicant, and it is substantially higher than described in the application.

  Potency assay approach is reasonable.

- Manufacturing process has not been tested with patient cells.

- Costs involved will be high; this could be mitigated by insurance.

Value Proposition

- SSc-PAH is a progressive disease with average age of onset between 50-67 years and presents with extremely limited treated options. The current standard of care relies on vasodilators, but there are mostly ineffective and result in a high level of morbidity and mortality.

- Systemic sclerosis has limited treatment options. HSCT is a rescue therapy in those with rapidly progressive disease, but it is contraindicated in those with SSc-PAH or cardiac involvement due to poor outcomes in this cohort. SSc-PAH responds less well to standard PAH therapies. A therapy that could address the spectrum of SSc related morbidities would be important for those affected (comparatively small numbers as overall a relatively rare disease). This project aims to extend the option of HSCT in SSc by editing out MPO in neutrophil precursors, with the hope this will improve pulmonary hypertension (+/- other morbidities).

- The burden on the healthcare system is likely to be reduced. Current annual healthcare costs for SSc-PAH patients is > $200,000/year. The proposed therapy, which is potentially curative, could significantly lower the burden on healthcare and rescue patients from demise. This is likely to impact up to 1000 Californians currently suffering from the disorder.

- The proposed cell therapy involves the use of autologous HSPC that are gene-edited to permanently knock out myeloperoxidase using (CRISPR/Cas9). This treatment, if effective, offers the potential to cure this debilitating disease in patients with no alternative therapies that can treat the underlying cause of disease. There is a significant unmet medical need.

- The proposed therapy offers an improvement over the current standard of care by targeting underlying innate immune-system-derived damage pathways.

- The treatment would involve cell retrieval from patients, followed by gene editing, conditioning, and then a single infusion. While this would be an expensive and intensive regimen it would be a one-off and likely to be acceptable in terms of burden.

- The models chosen to assess the rationale are not relevant models to this disease, and they bias the results towards confirming the sponsor's hypothesis that MPO is a key mediator of pathogenesis. Most patients are already MPO-deficient and therefore, MPO is not likely to be a major contributor to disease. So the first major weakness is that there is likely to be no benefit to patients. The second major problem is that the proposed therapy will, in fact ,endanger these patients. The reasons that there is no transplant done on Ssc-PAH patients now is due to the risks to these patients. The conditioning regimen would be the same as what is done for transplant and would endanger the patients, causing increases in mortality. So the major weaknesses are lack of benefit and significant risks.

- Concerns about the huge cost and reimbursement.

Rationale

- The scientific rationale is supported by initial in vitro and in vivo data.

- Relevant animal models have been justified to assess activity and safety.

- The scientific rationale is supported by in vitro and in vivo data, although the relevance of the models is not completely clear. Interactions with FDA sought to establish relevance of the selected mouse models to recapitulate the human condition. This requires further clarification before proceeding and could impact the acceptance of an IND.

- Patients have immune complex-mediated disease, and it is not clear whether the cell therapy would be clinically effective for these patients and whether the disease target is targetable.

- The models chosen to assess the rationale are not relevant models to this disease, and they bias the results towards confirming the sponsor's hypothesis that MPO is a key mediator of pathogenesis. In fact, most patients are already MPO-deficient and therefore, MPO is not likely to be a major contributor (or any contribution) to disease.

- Concerns about the disease target.

- Significant concern about the rationale for the study. Pulmonary hypertension is a final common condition driven by a range of pathologies. There is not convincing evidence that PH in SSc is related to MPO. There is not convincing evidence that MPO drives pathology in SSc. In fact, the small amount of data published suggest SSc patients neutrophils are already deficient in MPO. The investigators present evidence that neutrophil extracellular trap (NET) levels are higher in SSc patients, but they do not show that the NETs in SSc are MPO dependent. Much NETosis is MPO-dependent, but MPO-independent NETs are well recognized and more likely to occur in autoimmune disease. While not measuring the pulmonary vasculature itself, a previous report suggests bronchiolar lavage MPO is not recordable in SSc. The finding that MPO positive neutrophils (a generic marker of neutrophils) are seen in the myocardium of a few patients with known SSc/PAH who died (not necessarily of this) is not convincing evidence of MPO activity playing a role

on the pathogenesis of the process.

- SSc patients with pulmonary hypertension have poor outcomes very early in the HSCT process- including induction phase and hemodynamic change. The applicants present no evidence that this acute risk period will be ameliorated by their product. They show no evidence that disease modifying activity from MPO knock-out will affect the processes that mediate the poor outcomes that often occur early on. It seems unlikely that vascular and cardiac remodeling will reverse in the immediate hours and days/weeks after the transplant by absence of MPO, and no evidence is provided that it will. Some of the poor outcomes in PAH relate to the conditioning regimen. This is unchanged in the presence of the modified cells. The models aren't testing the effect of the regimen/modified HSCT on subjects with established PAH. The models used/proposed are all pre-treatment (by way of necessity), and this is a limitation that requires very careful consideration/justification before any decision to proceed to a clinical trial. How can we be confident that the modified cell transplant does not pose the same acute risk as a usual HSCT to the SSc patients with PAH? It is noted in the pre-IND that the FDA were concerned that the models did not mirror human disease, and clarification of their relevance was sought for the IND.

- The models used demonstrate the role of MPO in PAH (hypoxia in mice and Sugen hypoxia in rats). Hypoxia is known to drive MPO release, so it is unsurprising that knocking down MPO ameliorates PAH in these models. However, the evidence that this target plays a role in SSc-PAH, which differs clinically and histologically from idiopathic PAH and is not associated with the known mutations that are involved in iPAH, is lacking.

Project Plan and Design

- The project plan has been designed based on feedback from a successful pre-IND.
- Good responses for pre-IND meeting.
- Potential risk and mitigation strategies are clearly outlined.
- The potency assay for CMC appears to be robust.
- A number of pre-clinical models confirm the role of MPO in driving pulmonary hypertension in those models. The models have limitations, e.g., no autoimmune pathology (unlike SSc), and the clear linkage of MPO to disease process in Scleroderma is not available.
- Planned work includes:
    - Toxicology and biodistribution of GLP compliant drug product.
    - Two in vivo studies - one efficacy study in mice and one rat study to explore effect of MPO KO in Sugen hypoxia model. There is little detail provided on either of these, no justification of numbers and no discussion of dose range for the efficacy of DP in the mouse study. The rationale for repeating the Sugen hypoxia model was a little unclear. Since the efficacy study in mice is the only efficacy study to model the effect of HSCT in disease, more details and a dose testing range would have been valuable. What end point changes would be meaningful? Is this a go/no go if it doesn't meet specific criteria? A plan for a more severe phenotype model would be appreciated.
    - Establishing a potency assay - details on the enzymatic assay are needed. Flow and ELISA additionally are proposed but not details of how they will develop, define and validate these assays. It is difficult to therefore comment on feasibility over the time proposed for this work.
    - Drug lot manufacturing to GMP and stability testing.
    - Clinical trial planning.
- Generally, the project plan and design will position the team well for submitting their IND to the FDA. There were a few questions regarding the CMC activities which the applicant responded to. They are listed below.

- The applicant clarified the cells to be used for the evaluation of the gene edited frequency for multi-factorial potency assay in development.
- The applicant clarified a question regarding the evaluation of drug product potency NETosis assay. There is a plan to develop the assay during early clinical development with the intent of having it validated in time to be a potency assay for late stage clinical evaluation, addressing the reviewer concern.
- Regarding the lot release criteria, the acceptance criterion for gene editing is greater than or equal to 10%. It was unclear whether a 10% rate of knock-out will be sufficient to treat the PAH symptoms. In response to reviewer questions, investigators addressed this concern. They provided pilot run data showing consistent knock-out efficiencies of well over 80%. They will be revising the lot release acceptance criterion from 10% to 80%.

- Patients affected by the disease present with immune complex-mediated disease. It is unclear whether the proposed therapy will be able to impact the "target", and if it will be specific and effective clinically. The pre-IND feedback alludes to MOA, if the target has been completely defined and if the models are relevant to recapitulate the human condition.
- Detailed information is lacking to specifically address potential off-target assessments requested by the FDA.
- There is lack of clarity about the number of patients proposed to be enrolled in the phase 1 study involves. It is probably an accidental omission, but no pulmonary function is included in the outcome measures/schedule of evaluations on page 44.
- Would the clinical dose be altered if the equivalent (per kg) dose in mice didn't show effect on any parameters of PAH?
- Quality of life is proposed as an evaluation - will the authors use COMET-recommended quality of life score? Echo and right heart catheterization studies will be carried out and 6MWT. Time to clinical worsening (composite score)is used widely in trials for PAH and may be worth considering.

Project Team and Resources

- Team incorporates (a) world leaders in HSCT with track history of delivering new treatments in clinical trials (b) experts in MPO deletion and (c) expert clinicians in rheumatology.
- There is clinical expertise in PAH for the clinical trial. Team has extensive experience in gene editing and HSCT.
- The project team is experienced, including the developer of the therapy. This complemented by relevant expert consultants.
- Very strong team.
- This is a strong team of scientists and clinicians. Together they have extensive expertise in working with the FDA during the pre-IND and IND phase of clinical investigation (lead PI); expert understanding and experience in GMP manufacturing (applicant institution facilities), and mechanistic understanding of the role of MPO in SSc-PAH, as well as experience in working with models of this disease to evaluate the safety and potential for efficacy of the product, and in developing manufacturing protocols using CRISPR/Cas9.
- This team has extensive resources available to carry out all the proposed activities in this proposal.
- Competent team, each brings a different skill set and leadership. Sufficient for IND.

Population Impact

- Eligible population assessed. Consideration given to populations disproportionately affected by the disease

and mechanisms to maximize recruitment from these demographic groups.

- Justification is provided for the initial clinical population and sequentially expanded populations.
- Access and affordability activities as well as reimbursement and market access strategy are considered.
- Current treatment options are limited for SSc-PAH patients: use of vasodilatory drugs is the only treatment option, associated with high rates of morbidity and mortality. The disease also impacts women over five times more than men, with a more severe disease phenotype in African Americans, Asians, and Hispanics. The demographics have been well-considered indicating a diversity of patient populations affected by this disease with women potentially benefiting more from this proposed treatment.
- It seems that the investigators have a good understanding of the population demographics and realize that the populations that will receive the greatest benefit are women (5:1 ration compared to men) and African-American, Asian-American, and Hispanics, in whom the disease may be less frequent, but often more severe. They recognize that the narrow criteria for entry and the small sample size for the phase 1 clinical trial may impact the ability to reach these individuals.
- Access and affordability activities as well as reimbursement and market access strategy are considered.
- Patient advocacy planned for clinical trial design.
- Concerns about the huge cost.

Application #	PDEV-19201
Title (as written by the applicant)	Gene therapy to repair muscle function in GNE myopathy (GNEM)
Therapeutic Candidate (as written by the applicant)	Gene therapy to repair muscle function in GNE myopathy (GNEM)
Indication (as written by the applicant)	GNE myopathy – a rare muscle-wasting disorder caused by pathogenic mutations in the GNE gene.
Unmet Medical Need (as written by the applicant)	The current standard of care for GNE myopathy is limited to symptom management. There are no approved disease modifying therapies and no commercial development efforts for GNE gene replacement therapies using AAVs. This product has the potential to greatly impact the patient population.
Major Proposed Activities (as written by the applicant)	• Manufacturing scale-up to produce toxicology and GMP material • IND-enabling GLP toxicology study • Investigational New Drug (IND) application prep and submission to FDA
Statement of Benefit to California (as written by the applicant)	The project aims being conducted in California would benefit the Californian economy. GNEM patients in California also have the potential to receive benefit in the form of a viable treatment option.
Funds Requested	$4,791,375
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: 70

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	70
Median	70
Standard Deviation	3
Highest	75
Lowest	65
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	13

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

Key Strengths and Weaknesses

- There are several scientific limitations that temper confidence in full clinical translation. The most significant is the limited functional efficacy data: while biochemical correction (sialylation, proteinuria) is shown, the mouse models used do not reproduce the progressive muscle weakness seen in human GNEM, making it impossible to demonstrate rescue of clinically relevant functional outcomes such as strength or mobility. This restricts predictive validity for patient benefit. There is also heterogeneity in response among treated mice—some showing correction and others non-responsive—suggesting biological variability that is not yet mechanistically understood. Additionally, observed mortality in treated and untreated mice underscores model fragility and complicates interpretation of safety margins.

- Further scientific uncertainty arises from dose translation and long-term immunogenicity. The optimal human dose is extrapolated from murine ranges without confirmatory pharmacology in a larger species using the final construct. Although the proposed AAV reduces liver tropism, its novel nature means there is no existing human safety record, raising immunological unknowns that will need careful monitoring. Finally, while the proposed biomarkers (sialylation, MRI fat fraction) are biologically logical, the link between molecular correction and durable clinical improvement remains inferential rather than empirically proven.

- The score is pushed to a non-funding one as the preclinical model doesn't have the functional defect the therapy is trying to correct.

  The variability in response for a given dose over a range of doses is of concern.

- Strengths: (a) Proposed activities are well aligned with FDA type B meeting (b) Thoughtful choice of promoter and vector; superior muscle tropism of vector (c) Strong team

- Weaknesses: Preclinical data was not robust.

- FDA feedback not adequately incorporated.

- Science is shaky.

Value Proposition

- No therapies available for GNE myopathy and associated with high morbidity and profound disability; urgent unmet medical need for therapies.

- No current FDA-approved disease modifying therapy.

- Other therapies are currently in development – mostly oral sialic acid / precursors – two of which look promising, and one slow-release drug is approved for use in Japan (by Ultragenx; the same failed Phase 3 in the US).

- The non-profit model comes with a commitment to keep the cost to $750K per treatment, which is reasonable compared to other gene therapies in the market.

- The plan frames the product as a one-time treatment that avoids chronic administration costs and aims to optimize vector design/manufacturing to lower per-dose production costs—plus a market-access strategy oriented to public/commercial payers and patient-advocacy partners. This is directionally strong, but final affordability will hinge on realized cost of goods and pricing benchmarks in neuromuscular AAV gene therapy.

- Slowly progressive myopathy so clinical trials will require prolonged analysis. Heterogeneity of presentation based on missense variants (based on geographical ancestry) – this was not well discussed. It remains to be seen if progression will become slower if the sialic acid / precursors are approved – further complicating clinical development and market space. Plus, risk profile of gene therapy versus well-tolerated orally-delivered molecules.

- The TPP sets stage-appropriate, clinically interpretable endpoints with safety thresholds. Preclinical data argue for disease modification (restored sialylation, histology/strength), and a one-time IV dose could

markedly reduce patient burden vs chronic supplements that failed to show robust benefit; however, durability and magnitude of functional change vs placebo remain to be proven in humans.

- Value needs to be demonstrated further in preclinical work.

Rationale

- Replenishing GNE function in GNEM is rational given that patients have loss of function variants and hyposialylation. IV route of administration seems reasonable for skeletal muscle transduction. AAV and promoter are good choices to increase muscle expression and minimize liver targeting and expression in non-muscle tissues.
- The indication–approach–route linkage is strong (enzyme replacement to correct hyposialylation), with FDA-aligned endpoints and population providing a sound clinical bridge. Key residual risks are typical for systemic AAV (immune memory limiting redose; affordability not addressed here) and will require early proof-of-mechanism on biochemical rescue (muscle sialylation) and signals on functional endpoints to confirm translatability.
- Interesting pharmacology and proof of concept work; appears stage-appropriate.
- Strengths include dose-setting nonclinical data, promoter/capsid selections supported by mouse and large animal biodistribution screens, and clear safety/PD monitoring plans. Limitations include first-in-human uncertainty around durability, redosing barriers (neutralizing antibodies), and hepatic/systemic toxicity risk inherent to systemic AAV—each acknowledged with concrete mitigations (NAb screening, muscle-specific expression, immunosuppression, close liver function monitoring).
- Preclinical data package is not robust: (a) Choice of the knockin mouse model: the surviving mice have normal muscle function and mild plus variable kidney involvement. Aside from not being able to assess muscle phenotypic improvement, these mice also have high levels of endogenous GNE (more than wild type; per Fig. 8). They showed enhanced mortality during pre-clinical testing. There was a high level of variability in expression levels post-treatment (per Fig. 8; in mid and high doses). (b) Muscle sialylation improvement was nice, but kidney levels were not as impressive. (c) Proteinuria correction, if any, was variable. (d) Longevity of expression study was done in a different mouse model and with a different AAV. Muscle expression did last long-term; i.e., through the one-year period of study.
- The nonclinical package needs further development to fill in the gaps.

Project Plan and Design

- The proposal meets or exceeds CIRM's expectations for efficient and effective progression to IND clearance. Risk management and operational readiness are particularly strong, while greater granularity in financial–timeline integration would enhance confidence in execution feasibility.
- PDEV activities are in line with FDA type B meeting (Dec 2024).
- Team conducted a Pre-IND meeting with the FDA; the comments themselves seem fairly benign and supportive but the approach (and questions asked) was a little non-traditional; I think also FDA is communicating a little bit of skepticism that this group is ready for the translational work although certainly some "wins" in the comments; clearly the FDA is trying to be extra supportive, but there do appear to be significant gaps. FDA even felt compelled in their additional comments to note that they should identify an minimally effective dose (MED) and No Observed Adverse Effect Level (NOAEL) in their animal studies.
- FDA had critical feedback on design of definitive safety/tox study, which the applicant does not appear to have implemented into their planned study. Specifically, applicant is still proposing what appears to be an inadequate evaluation of safety/toxicity or biodistribution (as FDA noted) such as insufficient scheduled sacrifices and insufficient list of tissues for biodistribution; overall, study does not appear sufficiently robust and this needs to be corrected.
- Recommend the applicant engage with a nonclinical and regulatory consultant to re-work their proposed

nonclinical development program (and study design); as proposed, appears to be significant risk that they will not generate sufficient data to initiate human studies.

- Expected more detail on the CMC development program, particularly given the breadth of comments received from the FDA, the applicant's stated hope of leveraging first in human data to support licensure (i.e., increased bar), and that they're proposing to conduct definitive animal studies.
- More attention is needed for activities in the nonclinical package.
- Would have appreciated a more robust discussion of risks and mitigations.

Project Team and Resources

- All senior investigators and partners have demonstrable experience in translating gene-therapy programs to the clinic. The NIH, Yale, and MD Anderson links provide depth in preclinical modeling and biomarker assays, while Dark Horse Consulting and SK Pharmteco contribute validated CMC and regulatory infrastructures. Together, these resources cover the full IND-enabling spectrum—scientific, operational, and regulatory.
- The PI is an experienced neuromuscular disease physician and is also involved in other clinical trials in GNEM. The MD Anderson collaborator brings unique strengths. Other team members and the team and their consultants have adequate experience.
- Appreciate that a non-profit is leading development.
- There may be gaps in the internal team and perhaps an over-reliance on external consultants, particularly on the CMC side; seems to be significant risk of cost over-runs without close management of contracts (and unclear who would be doing that project management work).
- Strong team.

Population Impact

- There are ~200 known patients in the US – but genomic datasets indicate that the real prevalence may be an order of magnitude higher.
- The trial population is scientifically and ethically appropriate for first-in-human study, and the engagement strategy leverages trusted community networks. The main area for improvement would be broadening recruitment beyond the U.S. and Israel to ensure representation of genotypic and ancestral diversity in this globally distributed ultra-rare disease.
- No discussion was made about the type of GNE variants and variable phenotypes and how that would be addressed in patient recruitment and clinical development.
- Appears adequate.

Application #	PDEV-19172
Title (as written by the applicant)	Anti-miR-128 ASO, an antisense oligonucleotide therapy for heart failure and cardiac regeneration
Therapeutic Candidate (as written by the applicant)	A locked nuclei acid (LNA)-modified antisense oligonucleotide (ASO) designed to inhibit microRNA miR-128-3p
Indication (as written by the applicant)	Heart failure (HF) following myocardial infarction (post-MI HF)
Unmet Medical Need (as written by the applicant)	Heart failure after myocardial infarction is a leading cause of death, with no therapies that repair the heart. Current drugs only manage symptoms. Anti-miR-128 targets mitochondrial dysfunction, fibrosis, and impaired repair to restore cardiac function and address this major unmet need.
Major Proposed Activities (as written by the applicant)	• Preclinical Efficacy and PK/PD Studies in pig heart failure model • Completion of IND-enabling GLP toxicology and safety studies • CMC and IND preparation
Statement of Benefit to California (as written by the applicant)	Heart failure is a leading cause of death and disability in California, with high healthcare costs and few therapies that repair the heart. This project will advance anti-miR-128, a regenerative therapy that restores cardiac function by improving energy metabolism and reducing fibrosis. Success could improve outcomes for Californians with heart failure, lessen the burden on healthcare systems, and reinforce California's leadership in biotech innovation and translational medicine.
Funds Requested	$7,366,847
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: 70

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	68
Median	70
Standard Deviation	6
Highest	80
Lowest	60
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

Key Strengths and Weaknesses

- The proposed indication for the intervention is unclear (myocardial protection vs regeneration). Major concerns about the drug manufacturing process.
- CMC deficiencies. Premature project with significant planning deficiencies. Target patient population not well defined.
- Merit to the approach using a miRNA knockdown.

  Pre-clinical-to-clinical disconnect - the post MI dosing window in the relevant preclinical model (hours) and in patients (months) reflect quite different settings.
- Early-stage activities need to be better designed.
- Inadequate drug product development considerations and information is presented to justify large animal studies or GLP tox studies. The drug substance is unlikely to reach the target to produce a measurable biological effect.
- The main strength of the therapy is based on compelling nonclinical data in rodents and large animals that show cardiac improvement post MI. However, miRNA 128 is not a cardiac specific target and has known effects in the hemopoietic system and prostate. The potential for off-target effects could be substantial, and the data presented in the application did not demonstrate adequate safety in this regard.

  A large clinical study would be required to meet the program objectives.
- Strengths: exciting developments in miR space in heart failure.
- Weaknesses: lack of supporting preclinical data, unclear target patient population (subacute vs chronic), off target activity of the candidate.

Value Proposition

- Current standard of care (SOC) reduces symptoms but doesn't repair heart muscle or restore lost function.
- There is therefore a critical unmet need for regenerative therapies that can intervene after MI to prevent progression to HF by targeting the core biological mechanisms driving adverse remodeling and contractile dysfunction. The candidate therapy is uniquely positioned to address this gap by reducing fibrosis and inflammation, restoring mitochondrial function, and enhancing endogenous regenerative pathways to improve cardiac recovery and long-term outcomes. If effective, this therapy could benefit many patients post MI.
- Targeting a massive unmet medical need, i.e., post-myocardial infarction heart failure.
- The proposed treatment reduces burden to patients and providers by the injectable route. No hospitalization needed. The drug is easy to store and distribute; this is especially important for accessibility and use in community clinics. The candidate is cheaper to make.
- The team haven't defined the target population.
- Based on evaluation of proposed project plan and design below, it is difficult to see how the completion of the proposed CMC work by itself would provide an adequate basis for the FDA to allow the IND to be opened for treatment of human subjects.
- The planned administration up to two hours after myocardial infarction followed by monthly repeat dosing is clearly feasible in clinical practice.
- Questions: (1) Acute vs chronic treatment – acute delivery seems like a protective measure rather than a

regenerative therapy, (2) It's difficult to control outcomes; these are very much dependent on coronary intervention in patients with myocardial infarction. The drug will very likely require a megatrial to determine clinical utility. (3) Potential side effects of miR128 knock-down are not considered. For example, miR128 functions as tumor suppressor in prostate cancer, and in addition, it's key role is not only in pro-fibrotic TGFb signaling.

Rationale

- The design of early-stage activities has lots of pitfalls.
- The proposal does not seem to include data or rationale for why anti-miR-128 ASO is supposed to be biologically active in the proposed indication in any *in vitro* or i*n vivo* models. Such a rationale is typical before investing in expensive large animal efficacy studies or GLP toxicology studies.
- The proposed therapy directly targets the core biological mechanisms that drive progression from myocardial infarction (MI) to heart failure (HF). The scientific rationale is based on a number of preclinical studies in rodent MI models and a chronic large animal HF model that demonstrated significant increases in LVEF and reduced fibrosis compared with controls, showing reversal of maladaptive remodeling rather than temporary hemodynamic relief.
- Preclinical data in a Duchenne muscular dystrophy model support the hypothesis that these anti-miR128 ASO improve LVEF and reduce fibrosis. Small animal numbers and apparently notable differences at baseline complicate the interpretation of this data.
- Preclinical data (at 19-24 week follow-up) suggests safety. It's debatable whether this is sufficiently long follow-up; this needs to be clarified with FDA.
- Remarkable efficacy in suppressing the miR128 target in skeletal muscle, heart and liver are shown.
- Published data on miR128 in heart failure by the applicant is limited. Provided data is interesting, but it needs confirmation.

Project Plan and Design

- The overall plan appears robust and manageable within the allocated 30-month timeframe. To mitigate risk, the applicant has considered potential limitations based on timing of treatment of the therapeutic post-MI by defining the target optimal time to treatment between 2-18 hours. However, effectiveness of this therapy is dependent on coronary intervention post MI with potential for off-target effects in tissues other than the heart that have not been fully defined. Therefore, there are safety concerns.
- The target patient population isn't modeled by the in vivo model. What is the risk of prostate cancer?
- The team are not ready to formulate drug product, especially for GLP studies.
- This proposal seems to only include CMC work to prepare drug substance. There is no mention of any developmental work for drug product which is pharmaceutically compatible with human administration (no formulation studies, no filter sterilization studies to create a sterile injectable product, no container/closure studies, no clinical in use stability studies).
- While the proposed CMC work may be adequate to enable the proposed nonclinical studies, it is not enough CMC work to enable a successful IND to allow human administration. There has not been previous contact with FDA. If such contact had occurred, it is likely that FDA would have noted the need for drug product development studies outlined in the above comment. The drug substance part of this proposal is reasonable and should lead to the desired drug substance.
- The project is designed to be completed in 30 months to reach an open IND. The extent of the preclinical studies conducted to date limits the required development to three important tasks including 1) defining the optimal dosing frequency and pharmacokinetics/pharmacodynamics (PK/PD) in a relevant re-perfusion MI

model (already established).

2) cGMP scale up to meet the requirements of a GLP toxicology study and material translatable for an FIH study.

3) Conduct a GLP safety study in a preclinical model factored into the budget.

Concern that the miRNA targeted by the candidate is effective in other tissues. The main caveat of the proposal relates to effects on the prostate, immune cells and that the targeted mIR plays a more ubiquitous role in immune modulation.

- No INTERACT or preIND meeting with FDA, yet. This is planned for 2026.
- Large animal PK/PD studies to justify first in human applications are indeed important. The species needs to be confirmed and must be representative of the human adult heart.
- Toxicology studies are planned in two species.
- The study outline seems a bit premature. It is highly recommended to obtain advice from FDA before embarking on such studies, which appear to me underpowered and too short.
- The clinical study design is similar to first the cardiac miR study by Cardior/NovoNordisk (anti-miR-132) and should be appropriate.

Project Team and Resources

- Proposed team seems capable of performing the proposed work.
- Strong team.
- Strong expertise in miR and regulation of metabolism. Limited expertise in heart failure and post-MI studies.

Population Impact

- Outreach is not especially developed.
- Studies designed to include patients from diverse backgrounds to ensure access. Patient perspectives at planning stages to address barriers to participation.
- Strong impact.
- Demographics considered.

Application #	PDEV-19146
Title (as written by the applicant)	A Novel Non-viral DNA Gene Therapy for Calcium Pyrophosphate Deposition (CPPD) Disease
Therapeutic Candidate (as written by the applicant)	Double-stranded circular DNA construct encoding tissue non-specific alkaline phosphatase (TNALP)
Indication (as written by the applicant)	Calcium Pyrophosphate Deposition (CPPD) disease
Unmet Medical Need (as written by the applicant)	This therapy is the first disease-modifying treatment for CPPD, targeting its root cause and enabling infrequent, durable dosing. It should improve patient compliance and quality of life and offers potential long-term healthcare cost savings.
Major Proposed Activities (as written by the applicant)	• Optimization and large-scale manufacture of the Drug Product to support the proposed IND-enabling studies • Completion of IND-enabling studies to support safety, efficacy and tolerability of the Drug Product • Preparation and conduct of an IND meeting with the FDA
Statement of Benefit to California (as written by the applicant)	The proposed research addresses a major unmet medical need by developing the first disease-modifying therapy for CPPD disease, a debilitating condition estimated to affect ~300,000 older adults in California. By improving patient outcomes and reducing the burden on the healthcare system, it directly benefits California's aging population. The project also supports non-viral in vivo gene therapy innovation, strengthening the state's leadership in advanced therapeutic development.
Funds Requested	$12,909,553
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: 65

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	69
Median	65
Standard Deviation	8
Highest	85
Lowest	60
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	1
(1-84): Not recommended for funding	13

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in

the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

Key Strengths and Weaknesses

- Important platform addressing a major problem.
- Opportunity to test proof of concept of a novel modality with a targeted delivery.
- Unclear what the target population is. The need for this therapy is unclear.
- Significant work is needed for determining lead candidate, including optimal formulation.
- Absence of data that the technology will work.
- Small clinical trial with high dosage injection. No scalability, no FDA discussion, poor patient population identification, no cost discussion. Over-amplified down-sides of current treatment strategies.
- Applicants do not provide much detail to allow commercial aspects of product to be assessed in terms of how market demand may be addressed. Amounts of material required to treat large populations may be very large, beyond where current technology has been shown to be successful.

Value Proposition

- The value proposition is the potential for a better tolerated therapeutic especially for an elderly population that may halt progression of pseudogout.
- Novel gene therapy platform has potential to be more cost effective and have potential for re-dosing.
- Attacks a significant problem in the field of cartilage biology.
- Unmet Need: CPPD (pseudogout) is a common, debilitating crystal-induced arthritis affecting up to 7% of adults and 30% of those over 80. There are no disease-modifying treatments; current care is purely palliative (NSAIDs, colchicine, corticosteroids).
- Therapeutic Concept: Delivers tissue-nonspecific alkaline phosphatase (TNALP) via a proprietary DNA platform, enabling local, durable enzyme expression to hydrolyze extracellular pyrophosphate (PPi) — the molecular driver of calcium-pyrophosphate (CPP) crystal formation — thereby both preventing new crystals and dissolving existing deposits.
- Innovation: Non-viral, episomal, re-dosable circular DNA avoids the cost, payload limits, and immunogenicity of viral vectors. Enables repeat intra-articular dosing and long-term local expression with minimal systemic exposure. Potentially the first disease-modifying therapy for CPPD — with broad relevance to osteoarthritis and other joint calcification disorders.
- Societal Impact: Aging populations face growing CPPD prevalence; local, affordable gene therapy aligns with CIRM's emphasis on accessibility and affordability.
- Value proposition seems reasonable at a high level, but if the product has clinical benefit, it is not clear how much product is needed to satisfy the market, or whether it would be practical or cost effective to treat a large population. No attempt to define order of magnitude estimates is provided. Supplementary material provided indicates a preliminary plan to dose 12 patients three times, using about 40 mg of product per dose. While this is a reasonable assumption for a Phase 1 IND, it translates to large amounts (hundreds to thousands of kilos) required to treat 300,000 Californians, depending on dose and chronicity of repeat dosing. The technology to make DNA plasmids in E. coli is straightforward at modest scales needed for a phase 1 clinical trial, but it has never been attempted at the scale potentially needed for large markets. This brings an element of uncertainty to commercialization if successful.

Rationale

- Preliminary in vitro and in vivo data are provided with prototype compound supporting purported mechanism of action.
- Preliminary data support intended route of administration.
- Strong preclinical data supporting the rationale.
- Disease Biology: CPPD results from dysregulated PPi homeostasis—overproduction via ENPP1/ANKH and under-degradation via TNALP deficiency. Excess PPi combines with calcium to form CPP crystals that activate the NLRP3 inflammasome, driving inflammation and cartilage loss.
- Mechanistic Hypothesis: Restoring TNALP activity in the joint normalizes PPi levels and hydrolyzes existing crystals.
- Platform: A double-stranded circular vector with structural elements that enhance nuclear uptake and persistence, while minimizing innate immune activation. Demonstrated 10× potency improvement and durable transgene expression with low cytokine response in mice. Compatible with lipid-nanoparticle (LNP) delivery for scalable, non-invasive dosing.
- Feasibility Data: Intra-articular TNALP delivery achieved durable expression in murine joints.
- Scientific Rigor: Rationale supported by human genetics and animal data linking TNALP restoration to reduced crystal formation.
- Proposal contains no information to justify the therapeutic approach. Supplementary information provides evidence that the product is capable of transfecting mouse cells after IV administration, but not that the therapeutic hypothesis can be achieved. Information about the biological effects in vitro or in vivo of successful transfection in the proposed indication would be useful to evaluate rationale.

Project Plan and Design

- Early PDEV Activities: Optimization of TNALP construct and LNP formulation. Rodent CPPD model studies for efficacy (crystal dissolution, ALP activity, inflammatory biomarkers). Dose-response and biodistribution studies in mice.
- Late PDEV / IND-Enabling Activities: Large-animal safety and biodistribution in collaboration with Colorado State. GLP toxicology and repeat-dose safety studies.
- CMC: Process development and GMP production through GenScript and PNI/Cytiva.
- Regulatory Plan: INTERACT meeting planned during early PDEV; Pre-IND in Year 4.
- Clinical Protocol Draft: Phase 1/2 trial evaluating intra-articular delivery vs. microfracture control.
- Significant work is planned for determining lead candidate as well as optimal formulation.
- The project will rely heavily on the successful development of relevant animal models to assess activity.
- It will be important to have an early interaction with the FDA once the lead candidate has been selected to inform the scope of the IND enabling studies.
- The proposed safety pharmacology studies can be incorporated into the design of the toxicology study. Toxicity will likely need to be assessed in a weight bearing non-rodent species.
- Complex CMC with a combination product.
- It is difficult to evaluate efficiency when no assumptions are provided about how much drug substance and

drug product are needed to supply estimated project needs for supplies for clinical and nonclinical studies, process and analytical development studies, stability studies, and clinical in use stability studies. Submitters appear to rely on CDMOs to develop processes and make supplies under GMP with appropriate controls. Applicants do not appear to have had contact with FDA about a pre-IND discussion.

Project Team and Resources

- The team and consultants with respective responsibilities are well laid out to support all IND activities.
- Strong team - no concerns.
- Institutional Strengths: Applicant organization's integrated preclinical and manufacturing facilities; established partnerships with GenScript and Cytiva for cGMP manufacturing; strong scientific advisory network being built for CPPD clinical translation.
- Applicants seem to have experience in the proposed areas of effort. CDMOs identified seem to have relevant experience conducting the proposed activities. However, the level of detail provided by the applicant in the proposal does not allow for a clear understanding of the practicality of the proposed project plan, or to judge the resources required to implement it.

Population Impact

- Targets an elderly population with limited treatment options; addresses a major age-related burden in California.
- Local intra-articular administration minimizes systemic side effects, making therapy safer for older patients.
- Manufacturing model—cell-free DNA synthesis—offers lower COGS and scalable production.
- Planned partnerships with payors and patient advocates to ensure equitable access and affordability.
- Platform extensibility: same DNA architecture can be adapted for other joint diseases, expanding population benefit.
- Good discussion is provided on intended clinical study population.
- Good analysis of impact.

Application #	PDEV-19129
Title (as written by the applicant)	IND-enabling studies for a 2nd Generation Vaccine Targeting Glioblastoma
Therapeutic Candidate (as written by the applicant)	A vaccine designed to enhance the immune response against glioblastoma tumors expressing EGFRvIII.
Indication (as written by the applicant)	Patients who have a diagnosis of glioblastoma whose tumor has recurred and the tumor is known to be positive for EGFRvIII
Unmet Medical Need (as written by the applicant)	Glioblastoma is one of the most tragic tumors with an inexorable progression. After initial therapy, virtually all tumors return but no consensus exists for treatment as no therapy is consistently effective. As such, there is a major unmet need to develop a drug for recurrent glioblastoma.
Major Proposed Activities (as written by the applicant)	• To manufacture the drug under GMP conditions and confirm its safety. • To conduct extensive assays to confirm the activity of the drug and establish assays that will be informative for monitoring patients. • Obtain an IND from the FDA and formalize the clinical trial.
Statement of Benefit to California (as written by the applicant)	Glioblastoma has a very dire prognosis with only ~9% surviving 5 years. The incidence increases with age and those 65+ are the most affected. California has the highest population of 65+ in the US leaving a disproportionate impact on this state. An improvement in survival will lessen the personal and economic impact on Californians. If successful, our vaccine will also illustrate a new strategy for enhancing the effectiveness of vaccines that could be applicable to cancer or infectious disease.
Funds Requested	$5,029,306
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: 65

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	67
Median	65
Standard Deviation	8
Highest	80
Lowest	50
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	13

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel’s discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in

the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

Key Strengths and Weaknesses

- The pre-clinical model does not model recurrent disease and therefore does not support progression.
- There is a clear unmet clinical need improve the consequent morbidity associated with glioblastoma (GBM) and increase median survival which is less than 2 years.
- Very limited preclinical data are provided to support the potential for a significant clinical difference/benefit as compared to the previous product.
- The CMC is well planned. The applicant follows a CMC strategy used successfully with previous clinical trials.

  Previous clinical results were mixed and it does not seem likely that the changes proposed will lead to substantial efficacy.
- The key strength is in the design of the peptide and the innovative approach of taking proteasome processing into account. A major weakness is that the majority of animal studies lack therapeutic design. Vaccines were given on day 0. This is not predictive of therapeutic response. Similarly, given the history of other pepVIII vaccines in GBM and the weak preclinical data (mostly prophylactic), the value proposition is low. While the team has all the expertise to carry this study through, it is unclear if this will generate a meaningful improvement in patient survival. Better preclinical therapeutic designs should be performed and worked out before a clinical trial.
- The value proposition is questionable.

Value Proposition

- Glioblastoma is the most common brain tumor; it accounts for half of brain tumor cases.
- Current treatments are associated with limited survival.
- The proposed treatment is targeted to patients with recurrent glioblastoma, whose survival is limited to 6.2 months.
- The proposed treatment will be administered by intradermal injection and cost about $80 per dose. This would be relatively simple to administer and be accessible to a wide variety of patients.
- There is high unmet need in glioblastoma. The applicant has developed an optimized peptide vaccine against EGFRvIII. This vaccine builds on a previous version that had mixed results clinically.
- The proposed modality is simpler to administer as compared to e.g. CAR-T cell based therapies.
- The value proposition is low due to previous failure of peptide vaccines and prophylactic design of animal studies.
- Modifications to an earlier prototype peptide vaccine are intended to improve efficacy.
- Not likely to be efficacious.

Rationale

- Peptide cancer vaccines have largely been safe but have not shown sufficient clinical benefit.
- The applicant proposes a modification to a previous product that failed in prior clinical trials to improve

antigen presentation through more effective processing.

- Very limited preclinical data are provided to support the potential for a significant clinical difference/benefit as compared to the previous product.
- No specific data are provided to support the potential increase in activity based on combination therapy.
- No data are presented in the proposal to support synergy with bevacizumab for the proposed Phase I study
- Models for efficacy are not well designed.
- Justification for the indication and route of administration is well presented.
- Reviewing from the CMC perspective, the manufacturing plan is well designed and builds on experience with previous similar peptide vaccines used successfully in clinical trials. The FDA response to the pre-IND request was to refer to the acceptable IND from previous trials. In addition to the QC release assays and stability studies the applicant has proposed a information-only study further investigating the impact of stability/aging on potency which is well thought out and would be very helpful should they move forward to pivotal trials.
- Rationale is excellent, and there is an unmet need in GBM for therapeutics. However, the animal studies are weak and not predictive of response due to their prophylactic nature.

Project Plan and Design

- Manufacturing methods have been established and are ready for scale up.
- No studies are proposed to evaluate the combination regimen with the intended clinical product.
- The project needs better preclinical data.
- The proposed activities will facilitate an IND application.
- The plan appears reasonable and good, and builds on previous experience.

Project Team and Resources

- Team expertise is focused on the design and execution of the clinical trial.
- It is assumed there is sufficient expertise to prepare an IND, based on the antecedent vaccine.
- No concerns - this is a strong team.
- The proposed team of researchers is extremely well qualified to carry out the proposed studies.
- The team of consultants is extremely well qualified to support this project.
- Facilities and resources at the applicant institution are outstanding.
- The team has appropriate experience and the resources proposed appear reasonable.

Population Impact

- The need to address a diverse population has been considered.
- Good impact and plan.

- The applicants propose to over-sample Black and Latino individuals.
- The applicants propose to engage patient organizations and the local community to increase enrollment into the clinical trial.
- Efforts will be made to mitigate the costs of travel for the clinical trial (e.g., telehealth visits, reimbursement for travel).
- This is a small phase I trial in glioblastoma. The population impact appears reasonable.