Rady Children's Specialists of San Diego
A Medical Foundation

UC San Diego
SCHOOL OF MEDICINE

Advancing the future of pediatric healthcare…together.

Pediatric Neurology

12/20/23

Re: CIRM CLIN2-15085 grant “Personalized antisense oligonucleotide therapy for rare pediatric genetic disease: SCN2A”

Dear ICOC Governing Board/Application Review Subcommittee,

Our CIRM application CLIN2-15085 proposes a personalized antisense oligonucleotide therapy for the rare pediatric genetic brain disease SCN2A. Although the grant received a scientific score of ‘1’, meaning highly meritorious for funding, and met the published guidelines for the CLIN2 program in all regards, there were a number of issues raised at the Nov 28 2023 ICOC Governing Board (ICOCGB) meeting where answers were not immediately apparent, that let the committee to postpone a decision.

We would like to take this opportunity to address the main public concerns raised by ICOCGB members. The introductory comments are accurate, as SCN2A is a rare disease without current disease-modifying therapy. SCN2A encodes a sodium channel localized to the axon hillock, responsible for action potential propagation. The patient has a de novo toxic-gain of function mutation that causes the channel to open, leading to epilepsy and intellectual disability. The patient also has a healthy copy of the gene. Thus by silencing the toxic copy, cells will still have the healthy copy. This program is for an allele-selective ASO that will lead to degradation of the toxic copy. The drug has been developed and synthesized and is ready for administration to the patient, created by the n-Lorem Foundation, which has led discovery and development of quality ASOs based on over 30 years of experience and several marketed life-saving therapies including nusinersen for spinal muscular atrophy. The IND holder is Dr. Olivia Kim-McManus, a pediatric neurologist at UC San Diego Rady Children’s Hospital with dual subspecialty Board certifications in Epilepsy and Clinical Neurophysiology. Rady Children’s Hospital is the only Level 4 pediatric comprehensive epilepsy center in San Diego, and provides care for complex epilepsies to geographically, ethnically and socioeconomically underserved patients. Rady’s Child Neurology division is ranked 8th nationally, and considered among the top pediatric neurology programs in the country. This grant is for funds for 2 years to support the ‘n-of-1’ clinical trial in which the pre-treatment history will be compared with on-treatment outcome. The funds are to support the physician and study coordinator time, as well as the intrathecal drug

administration and outcome measures. As part of this grant, to increase diversity, we will also screen additional patients from under-represented groups that could benefit from this or similar drugs based upon rapid newborn whole genome sequencing at Rady Children's Institute for Genomic Medicine. CIRM will not be responsible for standard healthcare costs, drug costs, or neither will CIRM be in jeopardy of incurring costs beyond the terms of the grant, even if the drug is successful.

There were two main issues that seemed to be on the minds of the ICOCGB:

How does this effort advance CIRM's research mission?
According to FDA guidelines, N-of-1 clinical trials have two separate and often competing goals. The first is to produce clinical benefit for patients with severely debilitating or life threatening diseases. We agree that this goal is not in alignment with CIRM's mission, as this goal should fall to health care deliverers and/or insurers. The second goal is to advance research into novel therapeutics, where 'first in human' trials can often provide direct and convincing evidence of benefit. This second goal is the one we emphasize in our application, and unlike in standard placebo-controlled clinical trials (PCCT) where the goal is evidence of benefit *on average*, in n-of–1 trials the goal is evidence of benefit of a single patient. This second goal may be harder to achieve, but if the goal is met with demonstrated efficacy, then the effort can pioneer a potential precision therapeutics pathway for additional children in California with rare genetic conditions like SCN2A-associated developmental epileptic encephalopathy to reduce disease morbidity and mortality for all diagnosed individuals. This can reduce public health care costs as has been shown in other rare pediatric genetic conditions with existing FDA approved novel targeted genetic therapies like ASOs.

How does the effort expand for a broader benefit?
While it is still early days in n-of-1 clinical trials, there is a clear vision for how our study could impact the rare disease population specifically and the biopharmaceutical industry more broadly (PMID 21695041, 34551122). While not all drugs will have an immediate viable commercial path, even if clinical benefit is demonstrated, the n-of-1 approach can 'de-risk' future PCCTs once the potential for improvement is demonstrated. For the first time we have single major genetic causes identified in patients. These patients are fully genotypically and phenotypically characterized, and we are learning about the basics of how these patients progress to disease, how single gene mutations are modulated by pathways, and how plasticity of the CNS and other organs can impact response to targeted therapy.

In the case of SCN2A, Praxis Pharmaceuticals (https://praxismedicines.com/) is interested in developing commercial ASOs, and could be a future partner if this effort is successful. Indeed, an additional patient with a different SCN2A mutation treated with a different n-Lorem ASO is already demonstrating evidence of benefit. Once n-Lorem manufactures an ASO, that ASO is stable for years or decades, and the same drug could be offered to other patients with the disease or same mutation, especially as risk is reduced for each patient subsequently treated with the same drug. This also reduces costs, and allows n-Lorem to both help more patients, and assess clinical benefit across a broader range of patients. While the FDA caps at 30 the number of patients treated with any given drug, both

n-Lorem and for-profit biopharmaceuticals are taking an interest in future commercialization opportunities. The drug for FUS ALS has already transitioned from n-of-1 to an industry-sponsored PCCT, once enough patients were identified through genome sequencing to support future commercial pricing (NCT04768972). In the era of ever growing access to molecular diagnosis, likely many more programs that start as n-of-1 will demonstrate this potential.

Issues raised by ICOCGB verbatim from the transcript of the proceedings:
1.'The main concern of the science panel was the monitoring of the subject after treatment. Clinicians wanted there to be EEG monitoring of the seizures post-treatment…The current protocol asks for parent-reported seizures.'
Response. Please note the scheduled 24-hour EEGs are already incorporated into the protocol at each dosing interval (q3m), per schedule of activities as approved to the FDA (p.49). This has been included to assess for clinical benefit in addition to seizure diary, which is the current gold standard for seizure monitoring. The study investigators designed the study protocol to include EEGs for assessments pre- and post-treatment, including electrographic seizure quantification per Board-certified pediatric epileptologist as well as concurrent independent de-identified EEG analysis on a machine learning platform, including qualitative spectral analysis, spike quantification, and identification of potential neurophysiologic EEG biomarkers of disease. The patient has extensive existing natural history as a baseline, including long-standing monthly seizure diaries for countable motor seizures as well as prior inclusion in a national cohort of patients whose EEGs have been analyzed on a machine learning EEG platform. This will enable longitudinal assessments to detect change over time within the individual (i.e. study patient) for potential drug efficacy.

2. Ms. Duron: 'So we know that this is a problem that exists across racial/ethnic groups?'
Response. De novo mutations occur roughly equally across all racial and ethnic groups including Blacks, Latinos and Caucasians. This is because the mutation occurs de novo, and is not inherited from a parent, affecting all humans equally, documented in this reference, excepting that the Amish population may have slightly lower levels of de novo mutations, perhaps related to their isolated lifestyle (PMID31964835).

3. Ms. Duron ' How they got an 8.5 (score on diversity) if the researchers themselves can't identify that there's an racial/ethnic issue involved here.'
Response. Due to disease rarity and heterogeneity, there is limited disease specific demographic data. However the researchers and institution of record prioritize diversity and inclusivity in patient care and are committed to equitable patient access to clinical care and diagnostic genetic testing of all children presenting with developmental epileptic encephalopathies (DEE) due to rare genetic disease (such as SCN2A) who may benefit from similar types of gene therapy. Another aspect that may have led to the favorable DEI score is that our patient's symptoms were largely ignored by traditional medical approaches, wherein the seizures failed to respond to existing medications (PMID37460677). Our DEI score (diversity, equity, inclusion) reflects our commitment to the underserved which not only includes race,

ethnicity, but also the underserved population of DEE and intractable epilepsies, for which there are currently no available targeted therapies.

4. Ms Duron 'That shouldn't leave people out because they can't afford the cost [of genetic testing]. I'm a shade confused here'
Response. Ms. Duron is correct that there is potential genetic discrimination based upon financial as well as race, ethnicity, gender and other factors. The National Association of Genetic Counselors and the American Society of Human Genetics have policies to address these issues, and although it is beyond the scope of our grant to rectify this situation in California, our grant includes a sizable effort to ensure that genetic testing is offered to the underserved, in collaboration with the Rady Genomics Institute (see p. 15). This will increase the diversity of the population for whom this or other ASOs could be applied, to both stabilize/recover neurological function, as well as assess potential benefit in a larger group of patients, including those without means to enroll in clinical trials.

5. Dr. Duliege 'But I assume we are voting for allowing additional funds to the tune of less than $1 million to be given to finish the trial…. Its a supplemental funding'
Response. We would like to thank Dr. Duliege for this question. The application is for a new first-in-human clinical trial of an ASO treatment for a rare neurodevelopmental disease. The trial design is an 'n-of-1' drug, meaning the patient will serve as their own control, using quantitative objective clinical data acquired before and after drug treatment. We hope this clarifies Dr. Duliege's question.

6. Dr. Duliege 'So then my question becomes more relevant and valid, which is I don't know of any intervention that can tackle a developmental delay when it has already happened. At best you can prevent progressional developmental delay. I don't think you can ever reverse one…But is there value in spending money on something I don't believe fan be achieved'
Response. The term NDD encompasses a large group of disorders caused by genetic mutations or environment that share disease onset during periods of ongoing brain maturation and development. A critical factor is that brain maturation is not complete until the end of adolescence, so correcting genetic mutations can advantage intrinsic plasticity and resilience in the human brain, especially when coupled with therapy (PMID19109903). Studies in rodents document substantial reversibility of neurocognitive deficits if treatment is targeted to the underlying genetic mechanism. For instance, restoring expression of NF1, MECP2 or UBE3A can substantially improve cognition in mouse models of neurofibromatosis, Rett syndrome or Angelman syndrome. In these models, the earlier the correction, the better the outcome. While there are not sufficient studies to date on reversibility of human NDD with gene therapy, evidence is starting to accumulate, where we observe children regaining ability to walk or speak in therapy for spinal muscular atrophy, juvenile ALS, KAND or Angelman syndrome, to name a few (PMID35075293;PMID29091570). This is especially true in patients in which the brain is structurally normal, as in our subject who has always had an entirely normal brain MRI scan. In short, it is too early to conclude that NDDs have no chance of improved quality of life with targeted gene therapy. Importantly, in these examples, ASO therapy often provides the first evidence of reversibility, which then prompts further investment into other forms of therapy, as in

the example of spinal muscular atrophy includes both small molecule and viral gene replacement therapy.

7. Dr. Duliege 'I believe that if you stop a process such as intractable seizures, you can stop the progression of developmental delay'.
Response. Decades of clinical experience and dozens of studies support Dr. Duliege's assertion that seizures can both provoke as well as worsen neurodevelopmental delay. To the degree that seizures can be controlled with medication, further stasis or loss of developmental milestones can be prevented. Unfortunately, there are some genetic forms of epilepsy that are recalcitrant to current antiepileptic drugs, such as the developmental epileptic encephalopathy (DEE) displayed by our subject. Thus, the only feasible way to impact seizures is through targeted gene therapy. Because the patient's mutation activates the channel, an ASO approach to silence the toxic copy of the gene, while leaving the healthy copy intact, is well suited, and likely to impact seizures. The proof-of-concept approach for SCN2A ASO for such mutation was established in mice, which found dramatic evidence of improvement (PMID34850743). As documented in the grant, untreated SCN2A mutant mice presented with spontaneous seizures at postnatal day 1, and did not survive beyond postnatal day 30. Administration of the ASO to mutant mice reduced spontaneous seizures and significantly extended life span. Across a range of behavioral tests, Scn2a ASO-treated mutant mice were largely indistinguishable from WT mice, suggesting treatment is well tolerated. Because the mice were treated with ASO right after birth, it remains to be determined how much long-term permanent disability sets in at older ages. Our subject is still relatively young, yet the window of opportunity for dramatic clinical improvement may close soon. Of note, another SCN2A patient with a different mutation is currently being treated with an individualized ASO developed by n-Lorem Foundation. After 3 months of treatment this patient has seen a substantial reduction in seizures supporting the predicted mechanism of action.

8. Mr. Juelsgaard 'If you read the whole review that the GWG provided, there have been only nine people identified in the whole world with this condition, so extremely extremely rare.
Response. Mr. Juelsgaard is correct that there are only 9 individuals known carrying this exact patient's mutation, and probably only a subset of these could be treated with the exact same drug. It is a requirement of the FDA special guidelines for personalized ASOs that there be fewer than 30 patients in the world that could benefit from the drug in order to qualify for this program. However, SCN2A gain of function mutations are among the most commonly identified causes in intractable pediatric epilepsy, present in approximately 2-3% of patients meeting criteria for DEE. There are 304 patients with likely pathogenic and 335 patients with pathogenic SCN2A mutations in the ClinVar database of genomic variation correlated with human health. The degree to which this same drug could be used in other patients with DEE would depend not upon the specific mutation, but rather to whether patients with any toxic mutation in SCN2A carried the SNP to which the drug was designed on the toxic gene copy, estimated currently in the dozens. Please remember that response to the sickle cell gene therapy was initially reported in a single patient, in which the response was so dramatic as to prompt larger trials (PMID28249145). Thus while this drug is designed for a single patient, if the trial proves successful, we will learn that SCN2A toxic mutations can be amenable to ASO therapy, and thus

the same drug or similar drugs could be developed or advanced for other patients. This effort will thus not only support treatment for this single patient, but in the larger perspective, could lead to innovations in therapy across many patients and even potentially many different similar types of disease. We apologize if this was not conveyed adequately in the original submission.

9. Mr. Juelsgaard 'If this works, are we now bound to provide support for this person for the rest of their life'

Response. We wish to clarify that CIRM was not being asked to provide support for this subject's treatment but rather to fund the FDA-approved 2-year clinical trial to test the effectiveness of this drug with clinically validated endpoints, much like the many other clinical trials that CIRM already supports, excepting that this is an n-of-1 clinical trial. While n-Lorem commits to providing the drug to the patient 'for free, for life', and the CIRM grant would offset the trial costs, the costs for continued drug administration after the termination of what we hope will be a successful trial will fall to the patient's insurance and/or hospital. If the drug fails to reach desired endpoints, then it will be discontinued, and the patient will continue to receive standard care supported by their insurance and/or hospital.

10. Vice Chair Bonnevielle '...Just from a philosophical perspective, is CIRM going to continue to fund applications that come in that treat a single patient. …that calls into question whether how quickly we can get a strategy around a rare disease, how we fund rare disease…'

Response. While CIRM may want to develop a specific rare disease strategy, we wish to point out that our application meets qualifications for all requirements set out in the CLIN2 RFA, including inclusion and exclusion requirements. By partnering with n-Lorem Foundation Through our partnership with the n-Lorem foundation who discovered and developed an individualized ASO specifically for our patient, we will be able to treat this individual through an n-of-1 trial. We are hopeful that the patient will have a dramatic response to the drug. The FDA recognizes the potential for scientific advances in n-of-1 trials, as it supports testing a new drug directly in humans, where both the physician, IRB and family recognizes the favorable risk-benefit ratio. The FDA has codified this support in 4 draft guidance documents specifically written for the development of Individualized ASOs. The benefit of n-of-1 trials is that therapies that dramatically impact outcome will emerge. Given the advancement of whole-genome sequencing and genetic diagnoses, individualized therapies that show benefit in the pioneer (first) patient may have the potential to help other patients. In those cases, n-Lorem will help as many individuals as possible under the current guidance structure then partner to ensure any other patients can also gain access to the treatment. Certainly we have seen this in the case of FUS-ALS, where an n-of-1 treatment response was dramatically positive, prompting a major pharmaceutical company to fund a PCCT (NCT04768972). While it is too early to know if the SCN2A drug in our patient will yield such a dramatic response, certainly there is an expectation that many of the drugs applied to these ultra-rare patient groups, which target the genetic mutation rather than the symptoms, are going to change thinking about disease on a grand scale.

Importantly, Drs Kim-McManus and Gleeson, in partnership with n-Lorem, are committed to leveraging the outcomes of this trial to help CIRM shape their rare disease strategy. By having a real-time example of an n-of-1 patient being treated with a quality n-Lorem ASO under the

expertise and quality of care at Rady Children's Hospital, CIRM can further elucidate the value of treating a single patient and how the learnings from the single patient will be extrapolated to help other individuals with the same mutation, mutations in the same gene, or even other individuals with diseases caused by similar mechanisms.

11. Dr. Chark-Harvey ' I feel uncomfortable voting because I know what our mission is, but this is really a question around how do we enact that [mission] in this case.
Response. The mission of CIRM is 'CIRM's Mission: Accelerating world class science to deliver transformative regenerative medicine treatments in an equitable manner to a diverse California and world'. In our application we make the case as to why the trial we propose, to test a new first-in-class drug for a disease of huge unmet medical need, where the traditional medical system has failed, seems well in support of the mission. Beyond this single patient, the results of this research project will inform future studies, and could apply to more common diseases that affect larger patient populations. Moreover, of the 149 CIRM-funded clinical grants, the average award is $7.8M, often to test treatment in just a handful of patients. One CLIN2 award is for ~$12M to test gene therapy in just 6 patients. In this light, our proposal for ~$1M for a first-in-human drug that could transform thinking about NDDs closely aligns with costs per patient compared with existing funded efforts.

Additional Letters of Support, if requested, can be provided from:

LGS Foundation
CURE
Prosfoundation.org
Epilepsy Foundation San Diego
Beacon Biosignals
Praxis Pharmaceuticals
BIOCOM
Ionis Pharmaceuticals
Actio Biosciences
n-Lorem Foundation
Elizabeth Berry-Kravis

Sincerely,

Olivia Kim-McManus, M.D.
Associate Clinical Professor, UC San Diego Neurosciences
Neurology Section Vice Chief, Rady Children's Hospital
Rady Children's Institute for Genomic Medicine
Epilepsy and Clinical Neurophysiology

Joseph G. Gleeson, M.D.
Rady Professor, UC San Diego Neurosciences
Gleeson Laboratory
Rady Children's Institute for Genomic Medicine
Medical Director N-Lorem Foundation