An open-label single center, single participant study of an experimental antisense oligonucleotide treatment for *SCN2A* gene mutation

Regulatory Sponsor: Elizabeth Berry-Kravis, MD, PhD
Rush University Medical Center
1725 West Harrison Street, Suite 718
Chicago, IL 60612

312-942-4036
elizabeth_berry-kravis@rush.edu

Non-Profit Partner: n-Lorem Foundation
2888 Loker Avenue East, Ste. 110
Carlsbad, CA 92010
760-552-7113

Study Product: Experimental Antisense Oligonucleotide nL-SCN2-001

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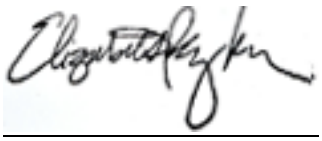
The signature below provides the necessary assurance that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH E6 Good Clinical Practice (GCP) guidelines.

Elizabeth Berry-Kravis

Printed/Typed Name of Investigator-Sponsor



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Signature of Investigator-Sponsor | Date of Signature

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List of Abbreviations and Definitions of Terms

Abbreviation	Definition
2′-MOE	2′-O-(2-methoxyethyl)-D-ribose
ABC-C	Aberrant Behavior Checklist – Community Edition
AE	Adverse event
ASA	American Society of Anesthesiologists
ASO	Antisense oligonucleotide
BFNIS	Benign familial neonatal-infantile seizures
BSID-3	Bayley Scales of Infant Development – Version 3
CBC	Complete blood count
CFR	Code of Federal Regulations
CK	Creatine kinase
CMAP	Complex motor action potential
CMP	Complete metabolic profile
CNS	Central nervous system
CSF	Cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
DSMC	Data safety monitoring committee
ECG	Electrocardiogram
EIEE11	Early infantile epileptic encephalopathy 11
EMG	Electromyography
EEG	Electroencephalogram
FDA	Food and Drug Administration
GLP	Good laboratory practice
GSV	Growth scale value
ICF	Informed consent form
ICV	Intracerebroventricular
IND	Investigational new drug
INR	International normalized ratio
IRB	Institutional review board
IT	Intrathecal
LFTs	Liver function tests
LP	Lumbar puncture
MRI	Magnetic resonance imaging
mRNA	Messenger RNA

NCS	Nerve conduction studies
nL-SCN2-001	nL00333; 2′-MOE ASO that selectively targets a specific region of the SCN2A pre-mRNA
ORCA	Observer Reported Communication Ability
PCR	Polymerase chain reaction
PI	Principal Investigator
PK	Pharmacokinetics
PO/PS	Phosphodiester/Phosphorothioate
PT	Prothrombin time
PTT	Partial thromboplastin time
RBS-R	Repetitive Behavior Scale – Revised
RUMC	Rush University Medical Center
SAE	Serious adverse event
SCN2A	Gene for alpha subunit of voltage-gated sodium channel Na(v)1.2
SD	Standard deviation
SNAP	Sural nerve action potential
SSP-2	Short Sensory Profile-2
U/A	Urinalysis
Vineland-3	Vineland Adaptive Behavior Scales – Version 3
WCS	Weighted Communication Scale

Protocol Summary

1 Synopsis

SPONSOR: Elizabeth Berry-Kravis, MD, PhD
TITLE: An open-label single center, single participant study of an experimental antisense oligonucleotide treatment for *SCN2A* gene mutation
INVESTIGATIONAL MEDICINAL PRODUCT: Experimental Antisense Oligonucleotide nL-SCN2-001
INDICATION: Refractory epilepsy, intellectual disability and autism related to *SCN2A*-encephalopathy
INVESTIGATOR STUDY SITE: 1 site
STUDY RATIONALE: Currently there is no standard therapy for SCN2A-encephalopathy other than symptom-based treatments (anti-seizure medications, medications targeting behaviors or movement disorders). The participant being treated with nL-SCN2-001 has a pathogenic de novo *SCN2A* mutation: c.5645G>A (p.Arg1882Gln, NM_021007.2). This single base substitution leads to a gain-of-function in the alpha subunit of the voltage-gated sodium channel Na(v)1.2, which plays an important role in the initiation and conduction of action potentials. *SCN2A* gain-of-function mutations cause early-onset severe epilepsies, while loss-of-function mutations cause autism with occasional seizures (PMID 29691040). The participant being treated has severe refractory epilepsy which has failed to be controlled by most available (>10) anticonvulsants. In this study an ASO to target a SNP that is phased to the pre-RNA transcript containing the mutation will be administered.
OBJECTIVES: **Primary Objective** To assess seizure frequency and/or length of seizures as documented with a seizure tracker. **Secondary Objective** To assess: • Improvement in adaptive behavior • Reduction in irritability • Improvement in excessive sensory sensitivities • Improvement in functional/cognitive ability

- Improvement in language
- Stabilization or improvement in EEG
- Reduction in potential toxicity from sodium channel blocking medications
- Safety and tolerability

ENDPOINTS:

Primary Endpoint

Change from baseline at 12 and 24 months post nL-SCN2-001 administration in seizure frequency and length of seizures with duration >10 seconds.
Number of seizures in past 3 months, average length of seizures in prior 3 months will be compared pre- and post-treatment.

Secondary Endpoints

Change from baseline at 12 and 24 months post-initiation of nL-SCN2-001 in:

- Adaptive behavior: Vineland Adaptive Behavior Scale Version 3 (Vineland-3): **yearly change in Growth Scale Value (GSV) scores from baseline to 12 months and baseline to 24 months for all subdomains: Expressive Language, Receptive Language, Written Language, Fine Motor, Gross Motor, Personal Daily Living Skills, Domestic Daily Living Skills, Community Daily Living Skills, Interpersonal Relationships, Play and Leisure, Coping Skills, relative to extrapolated yearly rate of change in GSV scores prior to treatment**
- Irritability and aberrant behavior: Aberrant Behavior Checklist – Community Edition, (ABC-C); Repetitive Behavior Scale – Revised (RBS-R); **change from baseline in ABC-C subscale scores for Irritability, Hyperactivity, and Stereotypy, and on RBS-R Stereotyped Behavior and Self-Injurious Behavior subscale scores**
- Sensory dysfunction: Short Sensory Profile-Version 2 (SSP-2); **change from baseline in Sensory Seeking subscale score**
- Cognitive and functional abilities: Bayley Scales of Infant Development Version 4 (BSID-4); **yearly change in GSV scores from baseline to 12 months and baseline to 24 months for Expressive Language, Receptive Language, Fine Motor, Gross Motor, and Cognitive Domains, relative to extrapolated yearly rate of change in GSV scores prior to treatment**
- Language and Communication: Observer Reported Communication Ability (ORCA) – administered at baseline, 6 months, 12 months, 18 months, 24 months; Weighted Communication Scale (WCS); **yearly change in Total ORCA Score and in WCS Structured, Unstructured, and Total scores at 12 and 24 months relative to extrapolated yearly change in scores prior to treatment**
- 24-hour EEG (if appropriate) – **change relative to baseline in quantitative frequency of ictal and interictal discharges on 24-hour EEG**

- Tolerance of phenytoin level < 20 ug/ml without seizures
- Safety and tolerability – tracking of adverse events and lab values

NUMBER OF PARTICIPANTS:

1 participant

INCLUSION/EXCLUSION CRITERIA:

Inclusion Criteria

- Genetically confirmed *SCN2A* mutation: c.5645G>A (p.Arg1882Gln, NM_021007.2)
- Ongoing refractory epilepsy at enrollment, minimum 4 seizures per month (averaged over 3 months prior to first visit)
- Treatment with at least one anti-seizure medication, with commitment to maintain stable dosing of anti-seizure medications during the study – adjustments may be approved by the PI, if clinically necessary
- Informed consent/assent provided by the participant (when appropriate), and/or participant's parent(s) or legally authorized representative(s)
- Ability to travel to the study site and adhere to study-related follow-up examinations and/or procedures and provide access to participant's medical records
- Ability/willingness to notify team of any adverse events

Exclusion Criteria

- Participant has any condition that in the opinion of the Site Investigator, would ultimately prevent the completion of study procedures or additionally contribute to epilepsy
- Use of investigational medications within 5 half-lives of the drug at enrollment
- Conditions that would make lumbar puncture or related sedation contraindicated or above standard risk (e.g. thrombocytopenia or other bleeding diathesis, space-occupying intracranial lesions, cardiorespiratory conditions increasing risk of the procedure, hemodynamic instability or inability to lay flat for the LP, infection of the skin of subcutaneous tissues near the lumbar puncture site)

DOSING, ROUTE, AND REGIMEN:

Dosing Regimen

A starting dose of 20 mg will be escalated after 28 days to 40 mg, then to a dose of 60 mg at 84 days followed by dosing of 60 mg every three months. If there is potential for increased clinical benefit, and if adequate safety has been demonstrated in the participant, the physician may choose to continue the escalation by 20 mg increments every 3 months, up to a maximum of 100 mg. Dosing will continue until the physician determines clinical benefit has been attained and as long as no adverse events are found. The maintenance dose will be adjusted at the discretion of the Principal Investigator. Dosing days will occur as in the SoA, unless

adjustments need to be made as per the Investigator. Once in the maintenance phase, the patient will receive the study drug at 60 to 90 day intervals, based on the Investigator assessment of whether clinical benefits are weaning towards the end of the dosing interval.

Dose Escalation Steps for nL-SCN2-001

PROPOSED REGIMEN*	STARTING DOSE (DAY 0)	STEP 1 (DAY 28)	STEP 2 (DAY 84)	STEP 3 (DAY 174)	STEP 4 (DAY 264)
Default	20 mg	40 mg	60 mg	60 mg	60 mg
Option 1	20 mg	40 mg	60 mg	80 mg	80 mg
Option 2	20 mg	40 mg	60 mg	80 mg	100 mg

* Refer to the paragraph above for criteria; “default regimen” should be followed if 60 mg provides adequate efficacy and safety; Options 1 and 2 should be followed for increased clinical benefit if safety allows.

Dose Modifications

The dose of nL-SCN2-001 would be reduced in a stepwise manner as depicted in the table below if the participant exhibits adverse events deemed as requiring dose reduction by the physician overseeing the study, with the objective of finding a well-tolerated dose which would then be maintained quarterly, as long as there is a potential for clinical benefit and no new adverse events are found.

If the participant continues to show undesired effects, subsequent dosing would then go to the next reduction step.

Dose Reduction Steps for nL-SCN2-001

DOSE*	STEP 1	STEP 2	STEP 3	STEP 4
60 mg	40 mg	20 mg	10 mg	Discontinue
40 mg	20 mg	10mg	Discontinue	N/A
20 mg	10mg	Discontinue	N/A	N/A

*If the dose was escalated to 80 mg or 100 mg, each reduction step would lower the dose by 20 mg, with the last step going from 20 mg to 10 mg, until stabilization or discontinuation.

The Investigator may then choose to attempt another dose escalation after 1-2 lower doses have been tolerated or choose to stop dose escalation if there is evidence of a favorable benefit-risk.

DURATION OF FOLLOW-UP:

This is an Investigator-initiated study for an Investigational New Drug Application (IND) to study the safety and efficacy of nLSCN2-001 in a participant with p.Arg1882Gln variant. The study is scheduled for 24 months in order to have enough time to capture potential cognitive,

language, and functional outcomes. If the participant does not exhibit Aes requiring the termination of the treatment, and if the physicians overseeing the study deemed it would be beneficial to continue, the participant would enter a long term follow up after 24 months.

STUDY DESIGN:

This is an interventional single center study to evaluate the safety and efficacy of an antisense oligonucleotide treatment with nL-SCN2-001 in *SCN2A* mutation, c.5645G>A (p.Arg1882Gln).

The participant will have access to treatment for life as long as the Investigator deems the treatment beneficial for the participant.

STATISTICAL METHODS:

Descriptive statistics and listings will be presented for all baseline assessments including participant demographics, disease history, general medical history, and selected endpoints. Unless otherwise specified, baseline is defined as the last available measurement taken on or prior to the enrollment.

Interval and ratio-level data will be summarized using descriptive statistics (number, mean, median, standard deviation [SD], minimum, and maximum). Ordinal and nominal-level data will be summarized using frequencies and percentages, and using contingency tables for associations, if appropriate.

For both primary and secondary outcomes, repeated measure continuous, interval and ratio-level data will be summarized using visualization and descriptive statistics (number, mean, median, standard deviation [SD], minimum, and maximum). Repeated measure ordinal and nominal-level data will be summarized using frequencies and percentages, and using contingency tables as well as visualization, if appropriate.

For the primary outcome of change in seizure frequency, we will evaluate the average 30-day seizure frequency from months 9-12 at 12 months and then from months 21-24 at 24 months compared to the baseline 3 months prior to dosing. The difference will be calculated. The goal is to achieve a 50% or greater reducing in seizure frequency with medication in order to justify continued dosing.

Introduction

2 Background Information

This study is being conducted to treat a child with *SCN2A*-related epileptic encephalopathy with an antisense oligonucleotide to knock down the mutated allele that is driving his disease. Currently there is no standard therapy for SCN2A related epileptic encephalopathy.

The participant being treated with nL-SCN2-001 has a pathogenic de novo *SCN2A* mutation: c.5645G>A (p.Arg1882Gln, NM_021007.2). This single base substitution leads to a gain-of-function in the alpha subunit of the voltage-gated sodium channel Na(v)1.2. The *SCN2A* gene encodes the voltage-gated sodium channel Na(v)1.2, which plays an important role in the initiation and conduction of action potentials. SCN2A is expressed in axon initiation segments and at nodes of Ranvier in myelinated nerve fibers (1). Voltage-sensitive sodium channels are heteromeric complexes consisting of a large glycosylated alpha subunit (approximately 260 kD) and 2 smaller beta subunits (33-39 kD). In most types of excitatory neuron, the Na(v)1.2 sodium channel is responsible for generating action potentials. The human *SCN2A* gene spans approximately 120 kb and has 29 exons, including a noncoding alternative first exon and alternative exon 6. Both inherited and de novo mutations are associated with disease in humans, ranging in severity from benign familial neonatal-infantile seizures (BFNIS) to early infantile epileptic encephalopathy 11 (EIEE11). Mutations in *SCN2A* can be categorized as loss-of-function or gain-of-function. *SCN2A* gain-of-function mutations cause early-onset severe epilepsies, often with severe cognitive, motor and language impairments, while loss-of-function mutations cause autism with occasional seizures (2).

De novo mutations in *SCN2A* are found in approximately 3% of early onset seizures (PMID 26993267). The p.Arg 1882Gln (R1882Q) allele is a recurrent allele which gives rise to a particularly severe form of developmental epileptic encephalopathy (DEE). The participants experience pre- or peri-natal seizures (“early-onset”), which occur at high-frequency and are accompanied by movement disorders and intellectual disability (2,3). As observed in other participants with early-onset SCN2A DEE, treatment with sodium channel blockers could improve seizures, but no improvement was seen in associated comorbidities (2-4). Electrophysiological recordings in heterologous expression systems reveal a gain of function phenotype for the R1882Q variant (5-7). A mouse model carrying this variant at the corresponding position showed a severe epileptic phenotype with heterozygous mice developing seizures as early as day 1 after birth and dying within the first month of life (8). Ex vivo electrophysiological recordings in cortical pyramidal neurons of heterozygous mice have shown an increase in neuronal firing, supporting the findings in heterologous cell lines (8). Increased neuronal activity at both cellular and network level has been observed for R1882Q iPSC-derived neurons at three weeks of differentiation (9). In this protocol an ASO targeting a SNP that is phased to the pre-RNA transcript containing the mutation will be administered.

The participant to be treated has severe intractable epilepsy uncontrolled by any currently known anticonvulsants. Trials of over 10 drugs have not produced control. He has cognitive, language and adaptive impairment and is non-verbal with an overall Adaptive Behavior Composite of 44 on the Vineland Adaptive Behavior scale (severe impairment), and age equivalents ranging from the 8-month level (Play and Leisure) to the 5 year level (Written Communication), scores in most domains centering around a 1-2 year age equivalency. His epilepsy is ongoing and impairing with 20-40 seizures per month and need for frequent rescue doses of anticonvulsants. He needs to maintain phenytoin at a high therapeutic level at all times, as levels below 20 ug/ml result in severe breakthrough seizures. Thus, there is an unmet need for better treatment to improve quality of life for this participant.

Nonclinical and Clinical Data

3 Nonclinical Data

In the absence of clinical data, insights into the potential safety profile of nL-SCN2-001 can be informed by the nonclinical toxicology program (see Module 2.4).

nL-SCN2-001 was administered once in the non-GLP studies, and once monthly for a total of 4 doses in the 13 week GLP study. The intrathecal route was used in rats as it is the proposed clinical route; in mice, due to anatomical challenges, the ICV route was used as it provides exposure to the CNS. In the non-GLP studies, a dose of 0.7 mg was administered in mice, and a dose of 3 mg was administered in rats. The findings in these two studies were limited to transient effects on gross motor function, which resolved within 24 hours. In the GLP-compliant study, nL-SCN2-001 was administered once monthly at doses of 0.3 and 1 mg/dose in rats via intrathecal injection. The study is completed, and the draft report is included in this submission. Changes were limited to transient non-adverse clinical observations with correlating neurobehavioral effects in alertness, gait, forelimb and hindlimb grip strength, tactile/touch/tail pinch reflex, body tone and body temperature. Non-adverse microscopic findings included macrophage vacuolation (meninges and nerve roots of the spinal cord, brain and meninges), nerve fiber degeneration in the nerve roots of the spinal cord (cervical, thoracic, lumbar, and injection site), mixed/mononuclear cell infiltration (meninges of the spinal cord and lumbar DRG), and an increased incidence and severity of tubular degeneration/regeneration and interstitial mononuclear cell infiltration as well as tubular basophilic granules in the kidney. Based on the absence of adverse findings, the no-observed-adverse-effect level (NOAEL) was considered to be the highest dose tested at 1 mg/dose.

4 Clinical Data to Date

This will be a first-in-human administration of nL-SCN2-001, therefore there is no prior clinical research data available. The dose and dosing regimen to be administered will be determined based on preclinical pharmacology, toxicology and pharmacodynamic (PD) observations.

5 Rationale

The participant to be treated has severe intractable epilepsy uncontrolled by any currently known anticonvulsants. Trials of over 10 drugs have not produced control. He has cognitive, language and adaptive impairment and is non-verbal with an overall Adaptive Behavior Composite of 44 on the Vineland Adaptive Behavior scale (severe impairment), and age equivalents ranging from the 8 month level (Play and Leisure) to the 5 year level (Written Communication), scores in most domains centering around a 1-2 year age equivalency. His epilepsy is ongoing and impairing with 20-40 seizures per month and need for frequent rescue doses of anticonvulsants. He needs to maintain phenytoin at a high therapeutic level at all times, as levels below 20 ug/ml result in severe breakthrough seizures. The participant has to go to the hospital twice per year for prolonged seizures requiring IV therapy. Thus, there is an unmet need for better treatment to improve quality of life for this participant. The severe epilepsy associated with the participant's p.Arg1882Gln mutation is expected to be predominantly mediated by gain-of function in the voltage-gated sodium channel Na(v)1.2 activity, resulting in excessive neuronal excitability. This is supported by the need to maintain phenytoin, an anticonvulsant with sodium channel blocking activity, at a high therapeutic level to keep the participant from having severe seizure exacerbations. Thus, selective knockdown of this gain of function allele should be the optimal way to reduce the overexcitability of the channel and control epilepsy. Selective knockdown also avoids the risk of knocking down both of the *SCN2A* alleles, which could have devastating neurological effects. The ASO to be employed shows good selective activity against the disease allele. It is known that haploinsufficiency of *SCN2A* is compatible with life and produces a much milder neurological condition than associated with the gain of function mutations, thus conversion from gain-of-function to haploinsufficiency with the ASO treatment is expected to result in overall improved functioning and quality of life even if not full normalization of function.

6 Risk Benefit Assessment

Potential benefits of treatment are expected to be reduction of seizures and epilepsy control with less dependence on high phenytoin levels, but potentially also improvement in the developmental trajectory of cognition, language/communication, and adaptive skills. The risks are those associated with lumbar punctures (LP) including headache, vomiting or post-LP syndrome after some LPs, and the risks known to be associated with intrathecal ASO administration including radiculopathy, ventriculomegaly, fever, vomiting and irritability. There is a theoretical risk of thrombocytopenia and increased urine protein, although less likely with an ASO delivered intrathecally as opposed to IV. Risks of anesthesia (if needed) are irritability when awakening,

vomiting, or remotely respiratory complications. Risks will be minimized by having highly experienced physicians performing the LPs, use of an atraumatic needle, careful dose escalation of the ASO with safety monitoring, and administration of anesthesia (if needed) by experts in pediatric anesthesia and by maintaining anesthesia time as brief as possible.
There is the risk of haploinsufficiency from knockdown of the mutated *SCN2A* allele, which itself is associated with the phenotype of seizures and autism. This phenotype is much milder than the gain of function phenotype and thus would represent a substantial improvement for this participant. There could be risk of normal allele knockdown, which would likely produce an adverse outcome however this is unlikely based on preclinical data showing an IC50 of 2.6 µM and 3.5-fold selectivity of this ASO for the pathogenic allele over the wild type SCN2A allele. It is highly likely that the benefits will outweigh the risks, given the severity of the current symptoms of the condition.

7 Known Potential Risks

Approximately 520 antisense oligonucleotides (ASO) were designed to bind to the mutated *SCN2A* pre-mRNA. Oligonucleotides were designed to promote selective degradation of the mutated *SCN2A* RNA through recruitment of Rnase H1 to the RNA-oligonucleotide heteroduplex (10). Oligonucleotides were designed as chimeric 2′-O-methoxyethyl/DNA modified oligonucleotides with five 2′-O methoxyethyl modifications on the 5′- and 3′- ends of the oligonucleotide and the central 10 nucleotides being deoxynucleotides (DNA). Oligonucleotides are a mixture of phosphorothioate, in which one of the non-bridging oxygen atoms is replaced with sulfur, and phosphodiester backbone.

The final *SCN2A* mutant allele targeting ASO, nL-SCN2-001, binds specifically to the mRNA of the mutated SCN2A pre-mRNA, resulting in the Rnase H1-mediated degradation of the mRNA, thus reducing production selectively of the mutated *SCN2A* protein. Homozygous knock out Scn2a -/- mice develop normally, but die perinatally from hypoxia and neurodegeneration, particularly in the brainstem (11). Heterozygous null mice have been reported to have altered hippocampal excitability, synaptic plasticity, and learning, as well as absence-like seizures (12,13). Thus, based on the allele-selectivity of nL-SCN2-001 and the doses proposed for the clinic, the reduction of total SCN2A will not exceed 50% and will be specific for the mutated sequence.

Since nL-SCN2-001 is a research drug, allergic reactions are possible.

To date, more than 10,000 participants have been treated with PS 2'MOE ASOs in controlled clinical trials and commercially. After intrathecal administration, PS 2'MOE ASOs distribute broadly throughout the spinal cord and CNS and have been shown to be pharmacologically active equally broadly. The most extensive experience is with nusinersen (Spinraza). Commercially, more than 10,000 participants have been treated with nusinersen, some for as long as 9 years. In addition, other 2'MOE ASOs have also been studied in multiple clinical controlled trials at a range of doses (10-120 mg) and a broad range of ages from

newborns to > than 40 years of age (MAPT-NCT03186989, SOD1-NCT02623699, Htt-NCT02519036, SNCA-NCT04165486, LRRK2- NCT03976349, C9orf72- NCT03626012, ATXN2- NCT04494256, GFAP- NCT04849741, FUS- NCT04768972). There is substantial clinical trial experience with many other members of the PS 2'MOE chemical class administered intrathecally (14-21). HALOS is an additional relevant clinical trial that is evaluating the safety and tolerability of an intrathecally administered PS 2'MOE ASO (NCT05127226) in Angelman syndrome.

Certain ASO drugs have been associated with inflammatory effects, including increases in plasma chemokines or cytokines. In general, these effects are considered related to the proinflammatory effects of ASOs at high drug concentrations. In humans, influenza-like/ constitutional symptoms such as fever, chills, increase in body temperature, and arthralgias have occasionally been observed following parenteral administration of ASOs at high doses, mostly during the initial dosing period.

Transient absence of the patellar and foot reflexes after dosing are considered a well described, non-adverse class finding for ASOs administered via IT injection (22) and the absence of any direct effects on respiratory, or cardiovascular parameters is consistent with previous experience of the ASOs of this chemical class (23). Ventriculomegaly has been observed with ASOs of this chemical class (24). Additionally, risks associated with the LP procedure (including post-dural puncture headache, infections, bleeding, and herniation) and risks associated with general anesthesia and/or sedation – which may be used for participant management during MRIs and LPs as determined by institutional guidelines – is associated with risks, such as nausea, vomiting and chills.

Overall, the risks, both identified and potential, associated with an allele-specific ASO are balanced by the anticipated benefits to the participant with a gain-of-function *SCN2A* gene mutation.

8 Minimizing Risks

Risks of the ASO will be minimized by careful dose escalation of the ASO with safety monitoring. The participant will be closely monitored for signs and symptoms of neurologic and neuropsychiatric changes. Neurological examinations will be conducted following each IT injection during the study to monitor for potential changes in patellar and/or foot reflexes. Identified risks associated with the LP will be minimized by having highly experienced physicians performing the LPs, the use of small gauge atraumatic needles, aseptic procedures, assessment of signs and symptoms associated with increased risk of CNS infection and herniation, assessment for health conditions that increase risks associated with LP, assessment of platelets and coagulation parameters before each study drug administration and close participant monitoring during and after study drug administration. General anesthesia/sedation will only be used when deemed necessary by the Investigator and will be performed by experienced personnel and anesthesia time will be maintained as brief as possible.

9 Known Potential Benefits

Potential benefits based on the known mechanism of the participant's gain of function mutation in *SCN2A* are improved epilepsy control and improvement in synaptic physiology, potentially resulting in improved cognition, language, adaptive skills, and behavior.

10 Objectives and Endpoints

Primary Objective
To assess seizure frequency and/or length of seizures as documented with a seizure tracker.

Secondary Objective
To assess:

- Improvement in adaptive behavior
- Reduction in irritability
- Improvement in excessive sensory sensitivities
- Improvement in functional/cognitive ability
- Improvement in language
- Stabilization or improvement in EEG
- Reduction in potential toxicity from sodium channel blocking medications
- Safety and tolerability

Primary Endpoint
Change from baseline at 12 and 24 months post nL-SCN2-001 administration in seizure frequency and length of seizures with duration >10 seconds. Number of seizures in past 3 months, average length of seizures in prior 3 months will be compared pre- and post-treatment.

Secondary Endpoints
Change from baseline at 12 and 24 months post-initiation of nL-SCN2-001 in:

- Adaptive behavior: Vineland Adaptive Behavior Scale Version 3 (Vineland-3): **yearly change in Growth Scale Value (GSV) scores from baseline to 12 months and baseline to 24 months for all subdomains: Expressive Language, Receptive Language, Written Language, Fine Motor, Gross Motor, Personal Daily Living Skills, Domestic Daily Living Skills, Community Daily Living Skills, Interpersonal Relationships, Play and Leisure, Coping Skills, relative to extrapolated yearly rate of change in GSV scores prior to treatment**
- Irritability and aberrant behavior: Aberrant Behavior Checklist – Community Edition, (ABC-C); Repetitive Behavior Scale – Revised (RBS-R); **change from baseline in ABC-C subscale scores for Irritability, Hyperactivity, and Stereotypy, and on RBS-R Stereotyped Behavior and Self-Injurious Behavior subscale scores**
- Sensory dysfunction: Short Sensory Profile-Version 2 (SSP-2); **change from baseline in Sensory Seeking subscale score**

- Cognitive and functional abilities: Bayley Scales of Infant Development Version 4 (BSID-4); **yearly change in GSV scores from baseline to 12 months and baseline to 24 months for Expressive Language, Receptive Language, Fine Motor, Gross Motor, and Cognitive Domains, relative to extrapolated yearly rate of change in GSV scores prior to treatment**
- Language and Communication: Observer Reported Communication Ability (ORCA) – administered at baseline, 6 months, 12 months, 18 months, 24 months; Weighted Communication Scale (WCS); **yearly change in Total ORCA Score and in WCS Structured, Unstructured, and Total scores at 12 and 24 months relative to extrapolated yearly change in scores prior to treatment**
- 24-hour EEG (if appropriate) – **change relative to baseline in quantitative frequency of ictal and interictal discharges on 24-hour EEG**
- Tolerance of phenytoin level < 20 ug/ml without seizures
- Safety and tolerability – tracking of adverse events and lab values

Study Design and Dose Rationale

11 Overall Design

This is an interventional open-label single participant study to evaluate the safety and efficacy of antisense oligonucleotide treatment with nL-SCN2-001 in *SCN2A* mutation, c.5645G>A (p.Arg1882Gln).

Prior to enrollment, informed consent will be obtained from the participant's legal representative, including the date and signatures. After informed consent has been received, the participant will undergo all baseline assessments listed in Schedule of Activities (Section 56) to confirm eligibility and obtain pre-dose measures for all assessments.

The study is scheduled for 24 months. If the participant does not exhibit Aes requiring termination of treatment, and if the physicians overseeing the study deem it beneficial to continue, the participant will enter a maintenance phase after 24 months. All baseline assessments will be completed the day before or the day of the injection, but prior to the injection being performed. Safety data will be collected at baseline and on each injection visit. Efficacy outcomes will be collected every 3 months for the primary outcome and at 6, 12, and 24 months or 12 and 24 months for secondary outcomes. Secondary outcomes will be compared to baseline or to rates of change observed prior to treatment. Possible limitations of this design include insufficient time of follow up pre-treatment to capture accurate rates of change on cognitive, adaptive and language secondary outcome measures. Variability in participant performance may impact performance on secondary outcomes requiring participant participation such as the BSID-4 and the WCS. It is possible that developmental and cognitive change will evolve over many years and only part of this will be detected in the 24 months of this study. All the protocol procedures will be performed at Rush University Medical Center. The participant will have

access to the treatment through n-Lorem Foundation for life as long as the Investigator deems the treatment beneficial.

12 Treatment Goal(s)

The primary goal of treatment is to improve severely limiting symptoms of epilepsy by decreasing frequency and severity (length) of seizures.

Secondary goals are to improve adaptive, language/communication, and cognitive functioning, and to reduce aberrant repetitive, sensory, and maladaptive behaviors.

13 Dose Rationale

From previous clinical trial experience with PS 2'MOE ASOs administered IT, a starting dose of 20 mg was selected for this participant based on the similarity of potency of this ASO to others evaluated at this pediatric age, in this chemical class, using this design and route of administration, in addition to the severity of the participant's condition.

A starting dose of 20 mg will be escalated after 28 days to 40 mg, then to a dose of 60 mg at 84 days, followed by dosing of 60 mg every 3 months. If there is potential for increased clinical benefit, and if adequate safety has been demonstrated in the participant, the physician may choose to continue escalation by 20 mg increments every 3 months, up to a maximum of 100 mg.

To date, more than 10,000 individuals have been treated with PS 2'MOE ASOs in controlled clinical trials and commercially. After intrathecal administration PS 2'MOE ASOs distribute broadly throughout the spinal cord and CNS and have been shown to be pharmacologically active equally broadly.

14 End of Study Definition

The end of the study is defined as the time when the participant in the study completes the last visit or procedure as shown in the Schedule of Activities (Section 56).

Study Population

15 Inclusion Criteria

All of the following inclusion criteria must be fulfilled for eligibility:

- Genetically confirmed *SCN2A* mutation: c.5645G>A (p.Arg1882Gln, NM_021007.2)
- Ongoing refractory epilepsy at enrollment, minimum 4 seizures per month (averaged over 3 months prior to first visit)
- Treatment with at least one anti-seizure medication, with commitment to maintain stable dosing of anti-seizure medications during the study – adjustments may be approved by the PI, if clinically necessary
- Informed consent/assent provided by the participant (when appropriate), and/or participant's parent(s) or legally authorized representative(s)

- Ability to travel to the study site and adhere to study-related follow-up examinations and/or procedures and provide access to participant's medical records
- Ability/willingness to notify team of any adverse events

16 Exclusion Criteria

Participant will be ineligible for this study if they meet any of the following criteria:

- Participant has any condition that in the opinion of the Site Investigator, would ultimately prevent the completion of study procedures or additionally contribute to epilepsy
- Use of investigational medications within 5 half-lives of the drug at enrollment
- Conditions that would make lumbar puncture or related sedation contraindicated or above standard risk (e.g. thrombocytopenia or other bleeding diathesis, space-occupying intracranial lesions, cardiorespiratory conditions increasing risk of the procedure, hemodynamic instability or inability to lay flat for the LP, infection of the skin of subcutaneous tissues near the lumbar puncture site)

Treatment

17 *SCN2A* ASO Injection

nL-SCN2-001 will be administered as a 10 to 15 mL bolus over 1-3 minutes. A lumbar puncture will be performed in accordance with the RUMC standard of care.

Cerebrospinal fluid samples will be collected just prior to IT administration of the study drug. Up to 15 mL of CSF will be collected for analysis in the same procedure. Following CSF collection, the participant will receive a single 10 to 15 mL IT administration of study drug over 1 to 3 minutes using institutional standard techniques.

For the first injection, the participant will be admitted for an outpatient procedure to RUMC to have an MRI, nerve conduction studies/EMG, and the LP of nL-SCN2-001, all done under anesthesia. After recovery from anesthesia, the participant will be monitored post-injection in the clinical research center and admitted to the hospital overnight for monitoring. The participant will be discharged and seen in the clinical research center for the 24-hour post-dose assessment. For any subsequent injections at which an MRI will be obtained the participant will be admitted for an outpatient procedure to RUMC to have an MRI and the LP injection of nL-SCN2-001 done under anesthesia. After recovery from anesthesia, the participant will be monitored post-injection in the clinical research center until 6-hours post-dose. For injections associated with a dose escalation, the participant will be admitted for an outpatient procedure to the PACU at RUMC to have the LP injection of nL-SCN2-001. After recovery from anesthesia, the participant will be monitored post-injection in the clinical research center and admitted to the hospital overnight for monitoring. The participant will be discharged and seen in the clinical research center for the 24 hour post-dose assessment. For stable dosing not associated with an MRI or dose increase, the participant will be admitted for an outpatient procedure to the PACU (if

anesthesia is needed) or will be seen at the clinical research center (if anesthesia is not needed) at RUMC to have the LP injection of nL-SCN2-001. After recovery from anesthesia (if needed), the participant will be monitored post-injection in the clinical research center until 6 hours post-dose (this post-dose observation period may be shortened in the second year of treatment if adverse events have not been seen in the first year of dosing). The inpatient period may be prolonged if it is considered clinically necessary by the Investigator.

18 Sedation and Analgesia

Considerations for sedation and analgesia for this participant will reflect balancing comfort versus risk. Selection among agents for oral sedation or local analgesia will be at the discretion of Dr. Berry-Kravis. If anesthesia is used, in general, sevoflurane by mask will be used for LP injections without additional procedures. Propofol will be used when an MRI is obtained prior to the LP injection. Standard anesthesia monitoring will be employed if anesthesia is used. Lidocaine cream will be applied followed by 1% lidocaine subcutaneously for local anesthesia if general anesthesia is not used.

19 Route of Administration

Study drug nL-SCN2-001 will be administered intrathecally.

Intrathecal Access

Typically, a 22-gauge 2 inch or 3.5 inch atraumatic spinal needle will be used to reduce the risk of post-dural puncture headache. 24- or 25-gauge needles may be used if needed due to post-LP symptoms with the 22-gauge needle. Dr. Elizabeth Berry-Kravis will perform the majority of lumbar punctures. She has performed over 3000 LP infusions. Dr. Tamar Caceres has been trained by Dr. Berry-Kravis and has expertise in LP infusions and will also be available for performing these injections when Dr. Berry-Kravis is unavailable. Needle direction for puncture will be guided with surface landmarks. It is not expected that ultrasound or fluoroscopy will be needed, but this can be used if needed. The opening of the needle will be pointed caudally for the injection. The L3-L4 interspace will be preferentially used, although the L4-L5 or the L2-L3 spaces may be used depending on the optimum route for access.

For administration, the drug dosing syringe containing the ASO will be prepared by the RUMC infusion pharmacy under sterile conditions using a laminar flow hood, according to SOPs at the pharmacy. Polypropylene products will be used for dosing and CSF collection. Luer lock connectors will be used on syringes and needles.

20 Dose Escalation

A starting dose of 20 mg will be escalated after 28 days to 40 mg, then to a dose of 60 mg at 84 days followed by dosing of 60 mg every 3 months. If there is potential for increased clinical benefit, and if adequate safety has been demonstrated in the participant, the physician may choose to continue the escalation by 20 mg increments every 3 months, up to a maximum of 100

mg. Dosing will continue until the physician determines clinical benefit has been attained and as long as no adverse events are found. The escalation will be stopped if there is an adverse event due to the ASO, there are significant lab abnormalities that are probably or definitely due to the ASO, there is worsening of a physical or neurological exam parameter due to the ASO.

For injections after day 84, the dose will not be escalated if seizures are fully controlled (no more seizures and anticonvulsant medications have been weaned). If there are still seizures or requirements for anticonvulsants, the dose may be escalated by a 20 mg increment up to a maximum dose of 100 mg. The maintenance dose will be adjusted at the discretion of the Principal Investigator. Dosing days will occur as in the SoA unless adjustments need to be made as per the Investigator. Once in the maintenance phase, the patient will receive the study drug at 60 to 90 day intervals, based on the Investigator assessment of whether clinical benefits are weaning towards the end of the dosing interval.

Table 1: Dose Escalation Steps for nL-SCN2-001

PROPOSED REGIMEN*	STARTING DOSE (DAY 0)	STEP 1 (DAY 28)	STEP 2 (DAY 84)	STEP 3 (DAY 174)	STEP 4 (DAY 264)
Default	20 mg	40 mg	60 mg	60 mg	60 mg
Option 1	20 mg	40 mg	60 mg	80 mg	80 mg
Option 2	20 mg	40 mg	60 mg	80 mg	100 mg

* Refer to the paragraph above for criteria; "default regimen" should be followed if 60 mg provides adequate efficacy and safety; Options 1 and 2 should be followed for increased clinical benefit with respect to seizure control if safety allows.

Toxicity Management and Dose Modifications

21 Dose Modifications

The dose of nL-SCN2-001 would be reduced in a stepwise manner as depicted in the table below if the participant exhibits adverse events such as lab abnormalities, changes in physical/neurological exam or if there is a significant increase in seizures after a 3 month period of significant improvement, lasting 3 months (and suggesting perhaps too much suppression of SCN2A protein activity), deemed as requiring dose reduction by Dr. Berry-Kravis and any other physicians overseeing the study.

If there is an increase in impairment on multiple secondary measures without improvement in others, even with better seizure control, dose reduction may be considered on the chance that this is a manifestation of excessive reduction of SCN2A protein activity. After an initial dose reduction, if the adverse event continues, further dose reduction can be done. If there is resolution of the problem, then additional dose reduction will not be carried out.

If the participant continues to show undesired effects, subsequent dosing would then go to the next reduction step.

Table 2: Dose Reduction Steps for nL-SCN2-001

DOSE*	STEP 1	STEP 2	STEP 3	STEP 4
60 mg	40 mg	20 mg	10 mg	Discontinue
40 mg	20 mg	10mg	Discontinue	N/A
20 mg	10mg	Discontinue	N/A	N/A

*If the dose was escalated to 80 mg or 100 mg, each reduction step would lower the dose by 20 mg, with the last step going from 20 mg to 10 mg, until stabilization or discontinuation.

The Investigator may then choose to attempt another dose escalation after 1-2 lower doses have been tolerated or choose to stop dose escalation if there is evidence of a favorable benefit-risk.

22 Toxicity Management

Rare adverse events that have been associated with ASO intrathecal administration include sporadic low incidence of myelitis, radiculopathy, and hydrocephalus (20). Thrombocytopenia and renal toxicity found in some peripherally administered ASOs is highly unlikely in this case due to the low exposures expected with intrathecal administration and has not been observed in intrathecal programs to date.

The participant will be monitored for safety events by the study team and study Investigators. The schedule of safety assessments includes evaluation of Aes, physical examination, neurological examination, vital signs, ECGs, and safety laboratory testing. The participant will undergo standardized safety testing prior to each dose of nL-SCN2-001 to ensure suitability to undergo the lumbar puncture procedure. Potential systemic adverse events will be monitored using standard clinical measures of organ function. Additionally, should clinical observations suggest potential adverse events of concern, MRI evaluation may be performed at times outside those specified in the protocol. The possibility of excessive suppression of SCN2A protein activity will be monitored with seizures and measures of functioning. If there is a significant increase in seizures after a 3 month period of significant improvement, lasting 3 months, dosing reduction will be attempted to titrate to better levels of SCN2A protein function. If there is an increase in impairment on multiple secondary measures without improvement in others, even with better seizure control, dose reduction may be considered on the chance that this is a manifestation of excessive reduction of SCN2A protein activity.

23 Stopping Rules

The Investigator may suspend or terminate the study when:

- A serious life-threatening adverse event considered by the Investigator as related to the investigational medicine occurs
- There is no stabilization of neurological status during the treatment period
    - The treating physician may apply to extend the protocol by amendment if there is sufficient evidence of safety, if not efficacy
- The participant's neurological function appears to be adversely affected by the injections
- The treating team determines the benefit/risk ratio is not favorable, including the consideration of risks related to repeated LPs

The study will be paused if a SAE occurs that is deemed to be possibly or definitely related to the investigational drug. Full review by the Data Safety Monitoring Committee will be conducted prior to determining if dosing should be resumed. In the absence of SAEs, the investigational drug will be continued for 24 months. At that point, study Investigators will determine if criteria are met to continue treatment.

Adverse events will be periodically reviewed by the DSMC, and the study may be terminated at any time at the discretion of the DSMC after review of an adverse event.

The threshold for the primary outcome measure demonstrating improvement would be at least a 50% improvement in seizure frequency in months 9-12 of the study compared to the 3 months of baseline prior to drug initiation. Improvements in the developmental measurements in the first year are not expected but worsening of skills would be evaluated as a possible concern and dose reduction would be considered depending on the pattern of worsening.

If the primary outcome measure is not met at 24 months, ongoing treatment would be considered in the case that 1) the participant shows improvement in trajectory at 24 months (rate of GSV change relative to baseline rate of GSV change before treatment) in at least two domains of the BSID-4 or at least four subscales of the Vineland, or 2) there is an improvement of 0.5 SD or more in the ORCA score (this is the clinical meaningfulness threshold), or 3) there is a 25% improvement (decrease) or more in the score on the ABC-C Irritability subscale, or 4) multiple of these outcomes.

At 24 months, assessments will again be done for months 21-24 to determine if there is a sustained improvement in seizure frequency of 50% or more from baseline. Determination of ongoing treatment would depend on meeting this primary outcome or the alternate criteria for neurodevelopmental assessments, now comparing the 24 month assessment to the baseline assessment and evaluating trajectory as described above.

24 Preparation, Handling, Storage, Accountability

n-Lorem will supply nL-SCN2-001 to the RUMC infusion pharmacy. Drug supplies will be maintained in a secure, limited access storage area under frozen conditions. The Investigator/Pharmacist/study staff will be responsible for ensuring adequate accountability of all study drug provided to the participant. The Investigator/Pharmacist/study staff will dispense nL-SCN2-001 to the study participant according to the Schedule of Assessments (Section 56).

Accountability records will be utilized to record:

- Date received and quantity of study drug
- Date study drug dispensed
- Date quantity of used and unused study drug, along with the initials of the person recording the information

Unused study drug may be destroyed at the site per RUMC infusion pharmacy standard operating procedure (SOP).

25 Formulation, Appearance, Packaging, and Labeling

nL-SCN2-001 will be labeled at a minimum, according to the local regulatory requirements. Please see the pharmacy manual for detailed information about the packaging, labeling, formulation, and appearance.

Upon receipt of the study treatment supplies, an inventory will be performed, and a drug receipt log filled out by the person accepting the shipment. The designated study staff will count and

verify that the shipment contains all the items noted in the shipping invoice. Any discrepancies, damaged or unusable study drug in a given shipment (active drug) will be documented in the study files. The Investigator (Dr. Berry-Kravis) must be notified immediately of any discrepancies, damaged or unusable products that are received.

26 Product Storage and Stability

Until dispensed to the participant, all study drug will be stored in a securely locked area, accessible only to authorized infusion pharmacy staff or study personnel. To ensure stability and proper identification, the drug substance will not be stored in a container other than the container in which it was supplied.

nL-SCN2-001 will be stored under controlled frozen temperature at -20°C, protected from light, until needed for administration.

27 Preparation of nL-SCN2-001

nL-SCN2-001 will be solubilized in an appropriate diluent to the indicated dosage level under sterile conditions according to USP <797> by the staff of the RUMC. The injection volume may be adjusted based on the participant tolerability of the injection volume. Detailed preparation and administration for nL-SCN2-001 can be found in the pharmacy manual.

Study Procedures

28 Procedures for Screening and Enrollment

A signed and dated ICF will be obtained from the parent/guardian, after a thorough explanation of possible risks and benefits as well as discussion of all study procedures before screening procedures commence. Evaluations obtained as part of routine medical care and performed during the screening period may be used in place of the protocol-specific evaluations. The parents/guardians of the participant will acknowledge and agree to the possible use of the information from this study to inform other similar studies and as part of potential publications, by giving informed consent. After informed consent is obtained, the participant will be assigned a permanent Identification number.

29 Study Assessments and Procedures

Study procedures and their timing are summarized in the Schedule of Activities (SoA) Table 4 (Section 56).

30 Review of Medical History

All conditions and procedures occurring before informed consent is obtained will be recorded as medical history. Relevant portions of the participant’s medical history and medical management, including, laboratory and radiographic testing, nephrology treatment, and major medical events of interest, will be captured by the Investigator and updated in the screening/baseline CRFs and eCRFs in RedCap as applicable.

This should include, but is not limited to medical history relevant to disease symptoms and developmental information, as well as services and therapies:

- Basic demographics (date of birth, sex, race, ethnicity)
- Age-of-onset of symptoms and date of confirmatory diagnosis including recording of initial symptoms, date of confirmatory diagnosis
- Genetic testing results including parental segregation
- Developmental milestones and current developmental status
- Past and concomitant medical diagnoses and dates of onset/resolution
- Current and past (prior 6 months) medications
- Current non-medication therapies and interventions (e.g. Special education, therapies)
- Baseline physical examination
- Baseline neurological examination
- Seizure frequency and length for all types of seizures over past three months
- Seizure data from seizure tracker over past three years
- Prior cognitive assessments
- Results of relevant evaluations including:
    - Laboratory test results – blood, urine, CSF
    - EKG results
    - MRI results
    - NCV/EMG results
    - 24-hour EEG results
    - Results of assessments including baseline and pre-treatment BSID-4, Vineland-3, ORCA, WCS, ABC-C, RBS-R, SSP-2

31 Dosing Days

Prior to study drug dosing on Day 1, procedures will be performed as outlined in the Schedule of Assessments (Table 4).

The first administration of nL-SCN2-001 will be given at this visit, and the participant will be assessed for adverse events. Following the first dose of nL-SCN2-001, the participant will be observed for 24 hours post nL-SCN2-001 IT administration in a hospital setting. If severe aEs are observed during IT administration or during the post-IT observation period, at subsequent nL-SCN2-001 injections the participant will continue to be observed for 24 hours post nL-SCN2-001 IT. If the participant does not develop any severe aEs, the participant will be observed for 6-hour post-IT for their subsequent nL-SCN2-001 IT administrations at the same dose. If the dose is escalated the participant will be observed for 24 hours in the hospital setting after the new dose is given. The parent/guardians of the participant will be instructed to notify site personnel if they develop any aEs during this post-injection observation time period. After each dose, the participant will be observed to closely monitor for acute, serious adverse events precipitated by the administration procedure or by the ASO drug product itself (e.g., hemodynamic instability, severe hypersensitivity reactions/anaphylaxis, CNS adverse effects).

After a given dose level has been achieved, and administered without observable adverse events, less frequent vital sign monitoring will be permitted at the discretion of the Investigator. In the event that abnormalities are detected, then appropriate medical intervention will occur, including the possibility of hospitalization and/or subsequent testing. Additional testing may be performed per standard of care guidelines. In the unlikely event that a severe allergic reaction should occur, the medical and nursing staff will follow institutional anaphylaxis guidelines.

32 Sedation and Analgesia

Considerations for sedation and analgesia for this participant will reflect balancing comfort versus risk. Selection among agents for oral sedation or local analgesia will be at the discretion of Dr. Berry-Kravis. If anesthesia is used, in general, sevoflurane by mask will be used for LP injection without additional procedures. Propofol will be used when an MRI is obtained prior to the LP injection. Standard anesthesia monitoring will be employed if anesthesia is used. Lidocaine cream will be applied followed by 1% lidocaine subcutaneously for local anesthesia if general anesthesia is not used.

33 Intrathecal Access

Typically, a 22-gauge 2 inch or 3.5 inch atraumatic spinal needle will be used to reduce the risk of post-dural puncture headache. 24- or 25-gauge needles may be used if needed due to post-LP symptoms with the 22 gauge needle. Dr. Elizabeth Berry-Kravis will perform the majority of lumbar punctures. She has performed over 3000 LP infusions. Dr. Tamar Caceres has been trained by Dr. Berry-Kravis and has expertise in LP infusions and will also be available for performing these injections when Dr. Berry-Kravis is unavailable. Needle direction for puncture will be guided with surface landmarks. It is not expected that ultrasound or fluoroscopy will be needed but this can be used if needed. The opening of the needle will be pointed caudally for the injection. The L3-L4 interspace will be preferentially used, although the L4-L5 or the L2-L3 spaces may be used depending on the optimum route for access.

34 CSF Sampling

A total volume of up to 15 mL of CSF will be obtained at each dose administration, divided into multiple tubes, and frozen for possible future biomarker and PK studies. 2 mL CSF will be sent to a local lab for safety testing (protein, glucose, cell count). Blood and CSF specimens collected just before each injection at RUMC will be stored at -80° for possible future PK analysis.

35 Procedures for Treatment (1-24 months) and Follow-Up

Following completion of the Day 1 dosing, all study treatments will be administered as described in the below sections and procedures will be performed as shown in Schedule of Assessments (Table 4).

Follow-up visits to assess clinical status and adverse events may be conducted by the Investigator or a member of the study team by phone or videoconferencing and documented in

the participant's medical record and/or CRFs. The Investigator or a study Sub-Investigator or Coordinator will speak to the participant and caregivers to assess adverse events, current health status, and medications. If a medical event or clinical change of concern is noted, the Investigator will determine the need and level of urgency for an in-person evaluation and contact the participant's local primary care provider if necessary.

Maintenance dosing after initial loading doses will continue on a 2-3 month (every 60-90 days) interval at the Investigator's discretion according to the same protocol. The interval for dosing will be based on the length of initial seizure control after dosing, presence of a clear deterioration in control before the next dose and need to give rescue doses of Dilantin to manage seizures toward the end of the dosing interval. If based on these parameters, a pattern of "wearing of"" of the ASO is seen at 90 day dosing intervals, the interval may be decreased by up to 30 days (to 60 day intervals). If this pattern is not seen towards the end of dosing again, the interval would remain at 60 days. The dosing interval will not be decreased to less than 60 days (-7 day window). Each dose will be followed by 6 hours of post-dose monitoring (or 24 hours if dose is increased at the injection) and a follow-up visit done by call or videoconferencing 7 days (±3 days) post-dose. Each maintenance dose date will be anchored off the previous maintenance dose date. Therefore, if a maintenance dose takes place out of window (postponed), the following maintenance dose will occur every 60-90 days (-7 day window) days after the out of window maintenance dose. After each dose, the Investigator will review safety data to determine whether or not to continue with the scheduled dosing.

36 Unscheduled Procedures and Visits

An unscheduled procedure or visit may be performed at any time during the study at the participant's (or parent/caregiver's) request or as deemed necessary by the Investigator.

37 Physical Examination

Physical examinations will be conducted at visits as outlined in the Schedule of Assessments (Table 4). A complete physical examination will include recording, height, weight, and full body system check: examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, and vascular.

Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded in the appropriate electronic Case Report Form (eCRF) that captures medical history. Any changes from the pre-treatment, baseline physical examination that represent a clinically significant deterioration will be documented on the AE eCRF.

38 Nerve Conduction Study (NCS) and Electromyography (EMG)

A NCS (nerve conduction study) with F-wave analysis will be conducted before the first injection at baseline to characterize nerve function in *SCN2A*-associated disease given this is not known. F-wave analysis will be conducted while the participant is awake (not sedated). The

peroneal and tibial nerves will be tested in the same leg and the ulnar nerve will be tested in the same arm throughout the study; specifically, peroneal/tibial/ulnar complex motor action potential (CMAP; distal site only, 1-point stimulation), and peroneal/tibial/ulnar F-waves. The minimal F-response latency is to be recorded. The F-estimate is to be calculated to account for variable limb length and to help determine if an abnormality is due to a lesion in the proximal nerve segment.

While the participant is under anesthesia for the first injection (D1), a full NCS under anesthesia will be done to characterize underlying nerve and nerve root function prior to dosing with ASO. The NCS will include peroneal CMAP (3-point stimulation), tibial CMAP (2-point stimulation), superficial peroneal sensory nerve action potential (SNAP), sural SNAP, ulnar CMAP (3-point stimulation), and ulnar SNAP. A limited electromyogram (EMG) needle exam will be done to look for signs of denervation. The NCS and EMG will be repeated only if the participant develops clinical symptoms or exam findings suggestive of neuropathy or radiculopathy.

39 MRI of the Brain

A standard uninfused MRI of the brain will be obtained at Screening/Baseline, 3 months, 12 months, and then yearly to evaluate for changes in ventricular size that might indicate hydrocephalus.

40 Electrocardiogram

A single 12-lead ECG will be performed at the timepoints outlined in the Schedule of Assessments (Table 4).

41 Vital Signs and Growth Measurements

The following vital signs and growth measurements will be collected and recorded:

- Body temperature (route can be oral, tympanic, rectal, axillary, skin, or temporal artery), heart rate, respiratory rate, and blood pressure
    - Blood pressure and heart rate measurements will be assessed with a completely automated device–- manual techniques will be used only if an automated device is not available or if the participant is unable to hold still enough to register the blood pressure on an automated device
    - Blood pressure and heart rate measurements should be preceded by at least 5 minutes of rest as possible for the participant in a quiet setting without distractions (e.g. television, cell phone)
    - Vital signs including systolic and diastolic blood pressure and radial pulse rate and temperature will be collected on the schedule outlined in the Schedule of Assessments (Table 4)
- Height and weight will be obtained on the schedule outlined in the Schedule of Assessments (Table 4)

42 Clinical Laboratory Testing

Laboratory tests will be performed according to the Schedule of Assessments (Table 4). Laboratory test results (local) will be reviewed by the Investigator prior to any study treatment. The medical personnel performing the dose administration will review the platelet count before performing the lumbar puncture. Clinical significance of out-of-range laboratory findings is to be determined and documented by the Investigator/sub-Investigator who is a qualified physician.

Specific laboratory tests to be performed are listed in Table 3.

Table 3: Clinical Laboratory Tests

Serum Chemistry (CMP)	Hematology (CBC)	Coagulation	Urinalysis	Cerebrospinal Fluid Analysis
• Albumin • Blood Urea Nitrogen (BUN) • Calcium • Bicarbonate • Chloride • Creatinine • Glucose • Magnesium • Phosphate • Potassium • Sodium • Total Bilirubin • Total Protein • Alanine Aminotransferase (ALT) • Alkaline Phosphatase (ALP) • Aspartate Aminotransferase (AST) • Creatinine Clearance	• Hematocrit (Hct) • Hemoglobin (Hgb) • Red Blood Cell Count (RBC) • White Blood Cell Count (WBC) • WBC Differential • Absolute Neutrophil Count (ANC) • Platelets • Mean Corpuscular Volume (MCV) • Mean Corpuscular Hemoglobin (MCH) • Mean Corpuscular Hemoglobin Concentration (MCHC)	• PT • PTT • INR	• Color • Clarity/ Turbidity • pH • Specific Gravity • Glucose • Ketones • Nitrites • Leukocyte Esterase • Bilirubin • Urobilinogen • Blood • Protein • RBCs • WBCs	• Cell Count • Total Protein • Glucose

43 Exploratory Biomarkers

Any sample testing will be done in line with the consent of the participant and/or the participant's legally authorized representative(s). CSF samples for biomarkers will be stored for future research on assays that may index CNS functioning in *SCN2A*-associated disease, that may assess genetic correction in the participant, or that may assess effects of ASOs in general on CSF parameters. These samples will be stored for a maximum of 25 years. Samples will not be

labeled with information that directly identifies the participant but will be coded with the identification number of the participant (participant number).

44 Assessments to Assess *SCN2A*-Related Disease Manifestations

See Table 4 for a summary of the following assessments and scales. The assessments must be performed by a clinically qualified evaluator.

45 Seizure Tracker

The number and length of seizures are considered the primary outcome for this trial. This data has been collected by the family in a Seizure Tracker program for many years. The participant will continue to be tracked for number and length of seizures. Parents/caregivers will enter data into the Seizure Tracker daily to document number and length of seizures for each seizure type.

46 Vineland Adaptive Behavior Scales – Version 3 (Vineland-3)

The Vineland-3 is a valid and reliable measure of a perso''s adaptive level of functioning from birth to 90 years of age (25). It is commonly used in clinical care and research to measure the development and functioning of individuals with and without disabilities and has been discussed with FDA as an outcome for clinical trials. It is an informant-based measure that yields a composite score and domain standard scores in domains (and subdomains) of: Communication (receptive, expressive, and written adaptive language functions), Daily Living Skills (personal, domestic, and community skills), Socialization (interpersonal relationships, play and leisure time, and coping abilities), and Motor Skills (gross and fine motor skills). This structure corresponds to the 3 broad Domains of adaptive functioning recognized by the American Association of Intellectual and Developmental Disabilities (AAIDD, 2010). The Survey Interview Edition is administered to parents or caregivers using a semi-structured interview format. In addition to standard scores and age-equivalents, growth score values (GSVs, person ability scores) are available for all subdomain scores allowing reliable assessment of change even in those who floor the measure or appear to make no progress when using standard scores due to functional level far below chronological age (26). The Vineland-3 will be administered at Screening/Baseline, 12, and 24 months by the same administrator to the same parent/caregiver. Standard scores and GSVs will be recorded in the source documents and eCRFs.

47 Aberrant Behavior Checklist – Community Edition (ABC-C)

The Aberrant Behavior Checklist- Community Edition (ABC-C) is a 58-item parent/caregiver rating scale used to assess the severity of a range of problem behaviors commonly observed in individuals with intellectual disability across five dimensions or subscales: irritability, hyperactivity, lethargy/withdrawal, stereotypy, and inappropriate speech (27). Items are evaluated on a 4-point Likert scale ranging from 0 (not at all a problem) to 3 (the problem is severe in degree). The caregiver completing the assessment will remain the same at all applicable visits throughout the trial. The measure will be completed by the parent/caregiver at

Screening/Baseline, 6, 12, 18, and 24 months throughout the trial and scores on the subscales will be recorded in the source documents and the eCRFs.

48 Repetitive Behavior Scale – Revised (RBS-R)

The Repetitive Behavior Scale – Revised (RBS-R) includes six domains: ritualistic behavior, sameness behavior, stereotypic behavior, self-injurious behavior, compulsive behavior, and restricted interests (28). Every behavior falling into 1 of the above categories is rated from 0 (behavior does not occur) to 3 (behavior occurs and it is a severe problem). The total score ranges from 0 to 129. The caregiver completing the assessment will remain the same at all applicable visits throughout the trial. The measure will be completed by the parent/caregiver at Screening/Baseline, 6, 12, 18, and 24 months throughout the trial and scores on the subscales will be recorded in the source documents and the eCRFs.

49 Short Sensory Profile – Version 2 (SSP-2)

The Short Sensory Profile-2 (SSP-2) is a standardized questionnaire designed to help evaluate a chil''s sensory processing patterns including overarousal and hypersensitive behaviors in the home, school, and community (29). These questionnaires evaluate a chil''s unique sensory processing patterns and are used to help design intervention strategies. The Child SSP-2 designed for children ages 3–14 (86 items) is the specific form to be used in this study and will be completed by the caregiver. The caregiver completing the assessment will remain the same at all applicable visits throughout the trial. The measure will be completed by the parent/caregiver at Screening/Baseline, 6, 12, 18, and 24 months throughout the trial and scores on the subscales will be recorded in the source documents and the eCRFs.

50 Bayley Scales of Infant Development – 4th Edition (BSID-4)

The Bayley Scales of Infant Development-4 (BSID-4) is a standardized developmental assessment measure used by clinicians to evaluate key domains in early childhood development for individuals between 16 days of birth and 42 months of age (30). This measure has been used in intellectual disability out of the age range for use in typically developing populations when mental age falls in the range of the BSID-4 (31). The domains in the BSID-4 include cognition, language (subdomains receptive and expressive), and motor function (subdomains gross and fine). The BSID-4 will be administered to the participant by a trained psychologist. In addition to standard scores and age-equivalents, growth score values (GSVs, person ability scores) are available for all subdomain scores allowing reliable assessment of change even in those who floor the measure or appear to make no progress when using standard scores due to functional level far below chronological age. The BSID-4 will be administered at Screening/Baseline, 12, and 24 months by the same administrator. Age-equivalents and GSVs will be recorded in the source documents and eCRFs.

51 Observer-Reported Communication Ability (ORCA)

The ORCA measure is a parent-reported questionnaire developed at Duke University for the evaluation of expressive, receptive, and pragmatic communication skills of children with Angelman syndrome and can be applied to other individuals with severe ID and communication impairment due to other neurodevelopmental disorders. The measure provides a more granular assessment of communication impairment than provided by standard language scales used with the typical population, and thus allows detection of change in populations with severe impairment that would not be possible with standard language scales. The measure is designed to observe the overall communication ability of the participant from the perspective of their primary caregiver and consists of 84 questions with 70 behavior items within 22 concepts. The assessment considers the heterogeneity of communication modalities and assesses the individual's unique methods of communicating. The total ORCA score reflects the primary caregiver's assessment of the participant's ability to perform behaviors frequently and consistently, indicating the participant's total communication ability. The caregiver completing the assessment will remain the same at all applicable visits throughout the trial. The measure will be completed by the parent/caregiver at Screening/Baseline, 6, 12, 18, and 24 months throughout the trial and scores on the subscales will be recorded in the source documents and the eCRFs.

52 Weighted Intentional Communication Scale (WCS)

The Weighted Intentional Communication Scale (32-34) will be scored from a 22 minute semi-structured examiner/child play session, conducted remotely in the home by the parent/caregiver based on instructions given via Bluetooth headphones by an SLP trained to fidelity on administration of the measure, and videoconferencing with the parent/caregiver and participant throughout the assessment. The same SLP rater will administer the measure to the participant throughout the trial. The sessions will involve 12 minutes of structured play prompts designed to elicit a range of communicative behaviors (e.g., requesting, sharing of affect) and 10 minutes of free play with a standard set of toys. The play session will utilize 3 sets of developmentally appropriate toys and the toy sets will be counterbalanced across participants and visits. The sessions will be videotaped and the WCS scores coded from videotapes of the sessions, according to standard coding methods by a coder trained to fidelity on the measure. The WCS reflects both the frequency of child-initiated intentional communication and the developmental level of the means by which the intention is communicated. In particular, coding of child intentional communication will be based on the occurrence of three classes of behavior: 1) gestures or nonword vocalizations during which the child coordinated attention between the message recipient and an object or salient event; 2) conventional gestures (e.g., distal points, head nods, pantomime) with attention to an adult; and 3) symbols (i.e., spoken words or signs) that were used in a non-imitative manner. The score will be obtained by multiplying each intentional communication act by the following weights: nonverbal=1; single symbol=2; and multiple symbols=3. Previous research has indicated that the weighted variable is more sensitive to change over time than the unweighted variable and that growth in the weighted variable (but

not the unweighted variable) is linear, related to later level of social impairment in younger siblings of children with ASD and detects change in response to treatment (28-30). The WCS will be administered at Screening/Baseline, 6, 12, 18, and 24 months. Scores on the structured session, unstructured session and total score will be recorded in the source documents and the eCRFs.

53 24-Hour Inpatient EEG Monitoring

Standard in-participant EEG monitoring will be done at RUMC for 24 hours prior to the first injection. This will be repeated pre-injection at 6 months, 12 months, and 24 months. Frequency of discharges and changes in EEG background will be recorded.

54 Telephone Follow-Up

Study site staff will perform telephone follow-up contact with parents/caregivers at 7 days post-injection, as specified in the SOA to determine the condition of the study participant and to record medications and adverse events.

55 Concomitant Therapy

Any medication and non-medication interventions, supportive interventions, or concomitant procedures that the participant is receiving at the time of enrollment or receives during the study will be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Prior use of medications taken by the participant within 180 days prior to screening will be recorded by the Investigator or qualified designee, as well as medications taken by the participants during the study through the last visit. This will include all prescription drugs, herbal products, vitamins, minerals, special diets, and over-the-counter medications. Any changes in concomitant medications will also be recorded on the eCRF.

56 Schedule of Activities

Table 4: Schedule of Activities–- Timeline of Events for Study Participant

Study Period	**Screening/ Baseline**	**Initial dose**		**Follow-Up**	**Second dose**		**Follow-Up**	**Third dose**		**Follow-Up**	**Fourth dose**		**Follow-Up**	**Maintenance**		**Follow-Up**
Study Time	**D0**	**D1**		**D7[c]**	**D28[a]**		**D35[c]**	**D84[a]**		**D91[c]**	**D174[a]**		**D181[c]**	**Doses every 60-90 days[b]**		**7D[c]**
		Pre-Dose[d]	**Post-Dose[e]**		**Pre-Dose[d]**	**Post-Dose[e]**		**Pre-Dose[d]**	**Post-Dose[e]**		**Pre-Dose[d]**	**Post-Dose[e]**		**Pre-Dose[d]**	**Post-Dose[e]**	
Location	Hospital	Hospital		Home/ Call	Hospital		Home/ Call	Hospital		Home/ Call	Hospital		Home/ Call	Hospital		Home/ Call
Informed consent	X															
Review eligibility	X															
Medical history[f]	X[f]															
Treatment intervention history	X															
Concomitant medications	X			X	X		X	X		X	X		X	X		X
Physical examination	X	X	X		X	X		X	X		X	X		X	X	
Neurological exam	X		X		X	X		X	X		X	X		X	X	
Height/ weight	X				X			X			X			X		
Vital signs	X	X	X		X	X		X	X		X	X		X	X	
12-lead-ECG	X				X			X			X			X		
Seizure Tracker review	X				X			X			X			X		
24-hour inpatient EEG	X[g]													X[g]		
Vineland-3	X[g]													X[g]		
ABC-C	X[h]										X[h]			X[h]		
RBS-R	X[h]										X[h]			X[h]		
SSP-2	X[h]										X[h]			X[h]		
BSID-4	X[g]													X[g]		
ORCA	X[h]										X[h]			X[h]		

Study Period	Screening/ Baseline	Initial dose		Follow-Up	Second dose		Follow-Up	Third dose		Follow-Up	Fourth dose		Follow-Up	Maintenance		Follow-Up
Study Time	**D0**	**D1**		**D7[c]**	**D28[a]**		**D35[c]**	**D84[a]**		**D91[c]**	**D174[a]**		**D181[c]**	**Doses every 60-90 days[b]**		**7D[c]**
		Pre-Dose[d]	**Post-Dose[e]**		**Pre-Dose[d]**	**Post-Dose[e]**		**Pre-Dose[d]**	**Post-Dose[e]**		**Pre-Dose[d]**	**Post-Dose[e]**		**Pre-Dose[d]**	**Post-Dose[e]**	
Location	Hospital	Hospital		Home/ Call	Hospital		Home/ Call	Hospital		Home/ Call	Hospital		Home/ Call	Hospital		Home/ Call
WCS	X[h]										X[h]			X[h]		
Clinical lab tests[i]	X[i]				X[i]			X[i]			X[i]			X[i]		
Interim history	X	X		X	X		X	X		X	X		X	X		X
Study drug infusion		X			X			X			X			X		
CSF sampling[j]		X[j]			X[j]			X[j]			X[j]			X[j]		
Adverse event monitoring		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
NCS/EMG[k]		X[k]														
MRI of brain[l]		X[l]						X[l]						X[l]		

a. Visit window may be adjusted to +7 days to accommodate scheduling for the participant as well as the clinic for dosing and dose observations.
b. Visit window may be adjusted to -7 days to accommodate scheduling for the participant as well as the clinic for dosing and dose observations.
c. Visit day for all follow up visit will relate to the day the injection is actually done and will be done 7 days after the last injection with a visit window of ±1 day; visit will be conducted by phone call or videoconferencing with the Investigator, Sub-Investigator, or Coordinator although if conducted by Coordinator, Investigator, or Sub-Investigator must review any AEs.
d. Pre-dose assessments may occur on the days of dosing or 1-2 days prior to the scheduled dosing. Pre-dose assessments for first injection can be baseline/screening assessments if these are obtained within 1-2 days of dosing.
e. Post-dose assessments may be done on the day of dosing at 6 hours post-dosing (all injections after D1 at which there is no dose increase) or on both the day of dosing at 6 hours post-dosing and on the day after dosing at 24 hours post-doing (for first injection D1 and any other injection for which the dose is increased)
f. General medical history and assessments relating to primary and secondary endpoints prior to enrollment will be collected as part of the baseline history. See details regarding historical baseline data collection noted in Section 30.
g. Assessments are to be done at Screening/Baseline, 12, and 24 month visits. Vineland-3 and 24-hour ambulatory EEG may be completed within 14 days prior to injection day.
h. Assessments are to be done at Screening/Baseline, 6, 12, 18, and 24 month visits. These can be completed with parent/caregiver within 14 days prior to injection visit.

i. Clinical laboratory assessments include complete blood count (with differential), serum chemistry with liver panel, urinalysis, and coagulation factors as noted in Section 42.
j. CSF sampling will be conducted pre-dose of study drug administration, this will be done on the same day as dosing. CSF analysis will be conducted as noted in Section 34.
k. To be performed at baseline and only repeated if symptoms/exam indicating possible neuropathy or radiculopathy are seen.
l. A standard uninfused MRI of the brain will be obtained at Screening/Baseline, 3 months, 12 months, and then yearly to evaluate for changes in ventricular size that might indicate hydrocephalus.

Safety

57 Definition of Adverse Event

An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of medicinal (investigational) product, whether or not the AE is considered related to the medicinal (investigational) product.

An AE can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from Study Drug

58 Definition of Serious Adverse Events (SAEs)

A Serious Adverse Event (SAE) is any adverse event that, in the view of the Investigator, meets any of the following criteria:

- Results in death;
- Is life-threatening; that is poses an immediate risk of death at the time of the event;
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in a persistent or significant disability/incapacity;
- Results in a congenital anomaly/birth defect;
- Or based upon appropriate medical judgment, may jeopardize the participant's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]; the event itself may be of relatively minor medical significance [such as severe headache without any further findings]). Severity and seriousness need to be independently assessed for each AE recorded on the eCRF.

59 Events of Special Interest

For the purposes of this protocol, the following are considered an AEs of Special Interest (AESI):

- Hydrocephalus
    - Brain CT scan or MRI will be performed to rule out hydrocephalus if any two or more of these symptoms appear in the participant without any obvious other underlying reason:
        - Nausea and vomiting;
        - Worsening of gait abnormalities;
        - Changes in behavior;
        - Worsening of seizures from recent baseline;
        - Poor appetite
    - If hydrocephalus is confirmed, the treatment will be stopped, and the participant will be addressed to a neurosurgeon to be treated according to the standard of care

60 Adverse Event Reporting and Recording

For this study, the study treatment follow-up period is defined as 30 days following the last administration of study treatment. The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up.

At each contact with the participant, the study team must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event section of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic, laboratory or procedure results should be recorded in the source document.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been ultimately determined that the study treatment or participation is not the probable cause. Serious adverse events that are still ongoing at the end of the study period must be followed up, to determine the final outcome. Any serious adverse event that occurs during the Adverse Event Reporting Period and is considered to be at least possibly related to the study treatment or study participation should be recorded and reported immediately.

61 Pre-existing Condition

A pre-existing condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

62 General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a pre-existing condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

63 Post-study Adverse Event

All unresolved adverse events should be followed by the Investigator until the events are resolved, the participant is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the Investigator should instruct each participant to report, to the Investigator, any subsequent event(s) that the participant, or the participant's personal physician, believes might reasonably be related to participation in this study.

64 Abnormal Laboratory Values

Any abnormal laboratory test result (e.g., hematology, clinical chemistry, or urinalysis) or other safety assessment (e.g., ECGs, radiology scans, vital signs measurements, physical examination), including those that worsen from baseline, that is considered to be clinically significant in the medical and scientific judgement of the Investigator and not related to underlying disease, is to be reported as an AE.

65 Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a pre-existing condition - surgery should not be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical Investigator

66 Assessment of Severity of Adverse Events

The Investigator will use the following definitions to rate the severity of each adverse event and serious adverse event.

- **Mild:** the event is easily tolerated by the participant; does not interfere with the participant's daily activities and require minimal or no treatment
- **Moderate:** the event results in more discomfort to the participant and causes some interference with functioning
- **Severe:** the event is incapacitating and interrupts a participant's usual daily activity - of note, the term "severe" does not necessarily equate to "serious"

67 Assessment of AE Relationship to Study Drug

The relationship of an AE to the Investigational Drug is a clinical decision by the Investigator or Sub-Investigator (SI) based on all available information at the time of the completion of the CRF and is graded as follows:

- **Not related:** a reaction for which sufficient information exists to indicate the etiology is unrelated to the study drug; the participant did not receive the study medication or the temporal sequence of the AE onset relative to administration of the study medication is not reasonable or the event is clearly related to other factors such as the participant's clinical state, therapeutic intervention, or concomitant therapy
- **Possible:** a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug but which could also be explained by concurrent disease or other drugs or chemicals; information on drug withdrawals may be lacking are unclear
- **Definite**: a reaction that follows a reasonable temporal sequence from administration of the drug, or in which the drug level has been established in body fluids or tissues, that follows a known or expected response pattern to the suspected drug, and that is confirmed by improvement on stopping or reducing the dosage of the drug, and reappearance of the reaction on repeated exposure (re-challenge)

68 Serious Adverse Event Reporting

The sponsor-Investigator will report to the FDA all unexpected, serious suspected adverse reactions according to the required IND Safety Reporting timelines, formats, and requirements. The sponsor should also report any serious adverse events to n-Lorem and will work with n-Lorem on any reporting to the FDA.

Unexpected fatal or life threatening suspected adverse reactions where there is evidence to suggest a causal relationship between the investigational drug and the adverse event, will be reported as a serious suspected adverse reaction. This will be reported to the FDA on FDA Form 3500A, no later than 7 calendar days after the sponsor-Investigator's initial receipt of the information about the event.

Other unexpected serious suspected adverse reactions where there is evidence to suggest a causal relationship between the investigational drug and the adverse event, will be reported as a serious suspected adverse reaction. This will be reported to the FDA on FDA Form 3500A, no later than

15 calendar days after the sponsor-Investigator's initial receipt of the information about the event.

Any clinically important increase in the rate of serious suspected adverse reactions over those listed in the protocol or product insert will be reported as a serious suspected adverse reaction. This will be reported to the FDA on FDA Form 3500A no later than 15 calendar days after the sponsor-Investigator's initial receipt of the information about the event.

The sponsor-Investigator must also notify the FDA in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting under § 312.32(c)(1)(i)-(iv).

69 Medical Monitoring

It is the responsibility of the sponsor-Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

Participant Discontinuation/ Withdrawal from the Study

70 When and How to Withdraw a Participant

The participant will be informed that they are free to discontinue study drug or withdraw from the study at any time and for any reason. The Investigator may discontinue study drug or withdraw the participant from the study if, in the Investigator's opinion, it is not in the best interest of the participant to continue the study.

The Investigator may terminate this study prematurely for reasonable cause provided that written notice is submitted in advance of the intended termination. If the Investigator terminates the study for safety reasons, the Investigator will immediately notify n-Lorem and subsequently provide written instructions for study termination.

71 Data Collection and Follow-up for Withdrawn Participants

The Investigator will work with the participant and n-Lorem to determine follow-up study visits and assessments after treatment termination. Ideally, if the participant discontinues nL-SCN2-001 early they will be encouraged to return within 3 months to collect efficacy endpoints and safety data. After that, study participation will end, and the participant can still return for regular clinical follow-up visits with the providers.

72 Study Termination

If the Investigator should discover conditions arising during the study that indicate it should be terminated, an appropriate schedule for termination will be instituted. The Investigator also reserves the right to discontinue this study for administrative reasons at any time.

73 Statistical Considerations

This is an interventional study in a rare genetic disease for a single participant.

A participant profile will be created using the data collected on the individual participant in the study. This will include, as appropriate, data listings, narratives, and graphical displays such as bar charts, spaghetti plots, and trend graphs over time.

Descriptive statistics and listings will be presented for all baseline assessments including participant demographics, disease history, general medical history, and selected endpoints. Unless otherwise specified, baseline is defined as the last available measurement taken on or prior to the enrollment.

Interval and ratio-level data will be summarized using descriptive statistics (number, mean, median, standard deviation [SD], minimum, and maximum). Ordinal and nominal-level data will be summarized using frequencies and percentages, and using contingency tables for associations, if appropriate.

For both primary and secondary outcomes, repeated measure continuous, interval and ratio-level data will be summarized using visualization and descriptive statistics (number, mean, median, standard deviation [SD], minimum, and maximum). Repeated measure ordinal and nominal-level data will be summarized using frequencies and percentages, and using contingency tables as well as visualization, if appropriate.

For the primary outcome of change in seizure frequency, we will evaluate the average 30-day seizure frequency from months 9-12 at 12 months and then from months 21-24 at 24 months compared to the baseline 3 months prior to dosing. The difference will be calculated. The goal is to achieve a 50% or greater reducing in seizure frequency with medication in order to justify continued dosing.

To investigate potential relationships between outcomes, correlations between changes over time will be examined.

Analysis and reporting for adverse events will be based on treatment emergent adverse events (TEAEs). Intensity and causality of TEAEs will be evaluated by the Investigator. A listing of all TEAEs will be provided including additional information such as action taken with study treatment, other action taken, and outcome.

Listings of laboratory parameters (hematology, chemistry, urinalysis) will be provided by study time point including changes from baseline. Any abnormal values will be flagged with ‘L’ for values below the lower limit of the clinical reference range and ‘H’ for values above the upper

limit of the clinical reference range and included in the listings. Listings of all vital signs, ECG and physical examination parameters by study time point will also be provided.

A safety narrative describing any death, serious adverse event, or other adverse event that is judged to be of special interest will be provided. Specifically, the safety narrative will include the clinical course of the event, with an indication of the timing of event corresponding to study drug administration; the nature, intensity/severity, and outcome of the event; relevant laboratory findings; any treatment administered for the event; action taken with respect to the study drug; and Investigator's assessment on causality. In addition, it should also include the participant's age, sex, race, height, and weight (if relevant), disease being treated and duration of disease, prior and concomitant medications, medical history, and active/ongoing medical conditions.

74 Handling of Missing Data

No imputation of missing data will be performed.

75 Data Handling and Record Keeping

All source data will be kept in study binders in locked rooms to which only study staff will have access. Participant study number will be used instead of name as possible. Data will also be in the electronic medical record at the site. This will have all the typical security protections applied to the electronic medical record system, however all data in the electronic medical record will be identified. Data will be entered in a secure REDCap database and only study staff will have access and logins to this database. This data will be shared with n-Lorem once de-identified. Information regarding the treatment of the participant may be published but the participant's name or identifiers will not be used. All tubes for sample storage will be coded with the participant study number.

Information about the participant will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed participant authorization informing the participant of the following:

- What protected health information (PHI) will be collected from participants in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research participant to revoke their authorization for use of their PHI

The parent/guardian of the participant will sign an authorization as noted above at entry into the study. In the event a participant revokes authorization to collect or use PHI, the Investigator, by regulation, retains the ability to use all information collected prior to the revocation of participant authorization. For a participant who has revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (long term survival status that the participant is alive) at the end of their scheduled study period.

76 Source Documents

Source data include all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, X-rays, participant files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. All original documents will be kept in a participant binder including paper CRFs and test booklets and result documentation. All documents in the source will be signed and dated. Clinical, procedure and laboratory, imaging and electrodiagnostic records will be kept in the electronic medical record at RUMC.

77 Case Report Forms

Electronic CRFs specifically designed for this study must be completed for the participant after providing informed consent. All participant data must have supportive original source documentation in the medical records or equivalent.

Data will be gathered in an Electronic Data Capture (EDC) system prepared by n-Lorem Foundation. n-Lorem hosted REDCap is a secure web application for building and managing online database. n-Lorem hosted REDCap will be used collect participant data and is compliant with 21 CFR Part 11, HIPAA it is specifically geared to support online and offline data capture for research studies and operations. The data collected on the eCRFs will be captured in EDC that meets the technical requirements described in 21CRF Part 11 (USA). The EDC will be fully validated to ensure that it meets the scientific, regulatory, and logistical requirements of the study before it is used to capture data from this study. Before using the EDC, all users will receive training on the system and study specific training. After they are trained, users will be provided with individual system access rights.

78 Study Records Retention

Paper records will be retained as long as the participant is treated which could be for decades. All records will be maintained during treatment and for 20 years following treatment. Records in the electronic medical record will be retained indefinitely.

The sponsor-Investigator will maintain records and essential documents related to the conduct of the study for the longest retention period that applies, based on all applicable regulations and requirements. These will include participant case histories and regulatory documents.

Appendix 1: Ethical, Regulatory, and Study Oversight Considerations

Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, ICH guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki.

Institutional Review Board (IRB)/ Independent Ethics Committee (IEC)

GCP requires that the clinical protocol, any protocol amendments, the informed consent, and all other forms of participant information related to the study and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific, and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent, and participant information, as relevant, will be obtained prior to the authorization of study treatment (first dosing).

Any substantial amendments to the protocol will require IRB/IEC approval before to implementation, except for changes necessary to eliminate an immediate hazard to participants. The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Protocol Amendment and/or Revision

Any changes to the study that arise after approval of the protocol must be documented as protocol amendments: substantial amendments and/or non-substantial amendments. Depending on the nature of the amendment, either IRB/IEC, Competent Authority approval or notification may be required. The changes will become effective only after the approval of the sponsor, the Investigator, the regulatory authority, and the IRB/IEC (if applicable).

Written verification of IRB/IEC approval will be obtained before any amendment is implemented. Modifications to the protocol that are administrative in nature do not require IRB/IEC approval, but will be submitted to the IRB/IEC for their information, if required by

Informed Consent of Participants

The Investigator or his/her representative will explain the nature of the study to the participant or his/her guardian or legal representative (if applicable) and answer all questions regarding this study.

Prior to any study-related screening procedures being performed on the participant, the informed consent statement will be reviewed and signed. A copy of the signed ICF will be given to the participant and the original will be placed in the participant's medical record. An entry must also be made in the participant's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the participant received a signed copy. The signed consent forms will be retained by the Investigator and made available (for review only) to the auditor regulatory authorities and other applicable individuals upon request.

Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating Investigators, their staff, and the sponsor(s). This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence.

All research activities will be conducted in as private a setting as possible.

Representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Appendix 2: References

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