NBI-921352 CLINICAL STUDY PROTOCOL

Amendment No. 2.0 Version Date: 30 November 2021

A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, Tolerability, and Pharmacokinetics of NBI-921352 as Adjunctive Therapy in Subjects with SCN8A Developmental and Epileptic Encephalopathy Syndrome (SCN8A-DEE)

Study No.: NBI-921352-DEE2012
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Development Phase: 2

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PROTOCOL AMENDMENTS

Protocol/Amendments	Date
Original Protocol	16 July 2020
Amendment 1	09 March 2021
Amendment 2.0	30 November 2021

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACTH	Adrenocorticotropin hormone
AE	Adverse event
ALT	Alanine aminotransferase
ASM	Antiseizure medication
AST	Aspartate aminotransferase
AUC	Area under the concentration versus time curve
AUC_{0-24}	Area under the concentration versus time curve for a 0 to 24 hour interval
$AUC_{0-24h,ss}$	Steady state area under the concentration versus time curve for a 0 to 24 hour interval
bid	Twice a day
CFR	Code of Federal Regulations
CGIC	Clinical Global Impression of Change
CGIS	Clinical Global Impression of Severity
CI	Confidence interval
C_{max}	Maximum observed drug concentration
$C_{max,ss}$	Steady state maximum concentration for a 0 to 24 hour interval
CNS	Central nervous system
CRO	Contract Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	Cytochrome P450
DCP	Diagnosis Confirmation Panel
DMC	Data Monitoring Committee
DSPV	Drug Safety and Pharmacovigilance
ECG	Electrocardiogram
EDC	Electronic data capture
EDTA K_2	dipotassium ethylenediaminetetraacetic acid
EEG	Electroencephalogram
eCRF	Electronic case report form
ET	Early termination
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration (United States)
FOS	Focal onset seizure
G-tube	Gastrostomy tube
GABA	Gamma-aminobutyric acid

GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GIC	Global Impression of Change
GIS	Global Impression of Severity
GTCS	Generalized tonic-clonic seizures
GOF	Gain-of-function
HAV-IgM	hepatitis A virus immunoglobulin M
HBsAg	hepatitis B surface antigen
HCV-Ab	hepatitis C antibody
HIV-Ab	human immunodeficiency virus antibody
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MES	Maximal Electroshock Seizure
Na_V	Voltage-gated sodium channel
NBI	Neurocrine Biosciences, Inc.
NOAEL	No-observed-adverse-effect level
PK	Pharmacokinetic(s)
qd	Once daily
QoLCE	Quality of Life-Childhood Epilepsy
QTcF	QT interval corrected for heart rate using Fridericia's correction
SAE	Serious adverse event
SAP	Statistical analysis plan
SSAS	Symptom and Seizure Activity Scale
SCN8A	Sodium channel, voltage-gated, type VIII, alpha subunit
SCN8A-DEE	SCN8A Developmental and Epileptic Encephalopathy Syndrome
SUDEP	Sudden unexpected death in epilepsy
TEAE	Treatment emergent adverse event
tid	3 times a day
[redacted]	[redacted]
Video-EEG	Video- electroencephalogram
VNS	Vagus nerve stimulator
VSD4	Voltage sensor domain IV

1. SYNOPSIS

Title of study: A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, Tolerability, and Pharmacokinetics of NBI-921352 as Adjunctive Therapy in Subjects with SCN8A Developmental and Epileptic Encephalopathy Syndrome (SCN8A-DEE)

Protocol number: NBI-921352-DEE2012

Phase of development: 2

Study center(s): Approximately 35 study centers in regions including, but not limited to, the United States, Europe, and Australia.

Objectives:

Primary

- To assess the efficacy of NBI-921352 as adjunctive therapy on the frequency of countable motor seizures (defined as generalized tonic-clonic seizure [GTCS], tonic, atonic or focal onset seizures [FOS] with noticeable motor component).

Secondary

- To evaluate the efficacy of NBI-921352 using the Clinical and Parent/Caregiver Global Impression of Change scales and the Clinical and Parent/Caregiver Global Impression of Severity scales.
- To characterize the pharmacokinetics (PK) of NBI-921352 and determine the effect of NBI-921352 on plasma levels of concomitant antiseizure medications (ASMs) and evaluated metabolites.
- To evaluate the safety and tolerability of NBI-921352.

Exploratory

- [redacted]

Methodology: This is a Phase 2 randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, tolerability, and pharmacokinetics of NBI-921352 as adjunctive therapy in subjects with SCN8A Developmental and Epileptic Encephalopathy Syndrome (SCN8A-DEE). Approximately 52 male and female subjects will be randomized for study participation according to the study eligibility criteria. Subjects will be randomized 1:1 (NBI-921352:placebo). This study will enroll approximately 52 subjects 2 to 21 years of age.

This study will include 2 separate cohorts:

- Sentinel Cohort: 8 subjects will be randomized into the Sentinel Cohort. These subjects will be considered a sentinel group to evaluate observed PK relative to predicted exposures as well as safety and tolerability. An external, independent Data Monitoring Committee (DMC) will review the Sentinel Cohort subject safety, tolerability, and PK data through the [redacted] titration period prior to randomization of subjects in the Main Cohort. Preliminary efficacy data will not be assessed as part of the interim Sentinel Cohort data review.
- Main Cohort: Once safety, tolerability, and PK have been assessed in the Sentinel Cohort, subjects will be randomized into the Main Cohort.

For both cohorts, this study will consist of 3 periods (for subjects who enroll in the separate, active extension study) or 5 periods (for subjects who do not enroll in the active extension study):

- An up to [redacted] screening period that includes a baseline period of at least [redacted] to collect baseline daily seizure diary data.
    - The baseline period may start once the investigator has confirmed that the parent/caregiver is capable of and comfortable with identifying seizures.
- A [redacted] titration period [redacted] at each of the 2 lowest titration dose levels and [redacted] at each of the 2 highest titration dose levels)
- A [redacted] maintenance period
- A [redacted] taper period (for those subjects not enrolling into the active extension study)
- A [redacted] safety follow-up period (for those subjects not enrolling into the active extension study)

Subjects will be eligible to enter the separate, active extension study if they have successfully completed 16 weeks of treatment [redacted] titration period and [redacted] maintenance period). Subjects in the active extension will receive active treatment; however, treatment received during Study NBI-921352-DEE2012 will remain blinded until the last subject ends their participation in Study NBI-921352-DEE2012 and the study database is locked.

Screening/Baseline Period – Sentinel and Main Cohorts

After informed consent has been provided by the parent/legal guardian or subject (if appropriate) and the subject has provided assent (if appropriate), subjects will be screened for eligibility to participate in the study. Prior to starting the baseline period, site personnel will review the seizure types with the subject and parent/caregiver and train them on correct seizure identification with a focus on identification of countable motor seizures [redacted] as well as noncountable seizures [redacted]. Methods of training may include recent [redacted]

The investigator will document that training has been completed and the parent/caregiver is capable of and comfortable with identifying seizures before the start of the baseline period. The investigator will also document that the subject has an adequate rescue medication regimen as well as a nocturnal alerting system in place. Baseline daily seizure diary data must be collected for at least [redacted], during which the parent/caregiver will complete the daily diary to record the number and type of countable motor seizures, as well as the occurrence of noncountable seizures for recording of seizure-free days. After completion of the baseline period, final eligibility will be confirmed by the investigator after review of the baseline diary data to ensure that parent/caregivers completed the diary according to instructions and that the subject has sufficient frequency of countable motor seizures (on average at least 1 countable motor seizure per week [4 per 28-day period]).

A sample for comprehensive genetic epilepsy panel testing will be collected at screening and used to verify the diagnosis. The clinical and genetic findings supporting the diagnosis of SCN8A-DEE will be reviewed and confirmed by an external Diagnosis Confirmation Panel (DCP) based on guidelines outlined in the DCP charter.

Rescreening is permitted if a subject does not meet all eligibility requirements and returns to be rescreened. A subject that has failed screening twice may not be rescreened again without prior permission from the Sponsor. Subjects who do not meet seizure frequency criteria as assessed during a completed baseline period will not be eligible for rescreening. Genotyping assessments do not need to be repeated for subjects who are rescreened.

Titration Period - Sentinel Cohort

The first 8 subjects will be randomized into the Sentinel Cohort in a 1:1 ratio (4 subjects to NBI-921352 and 4 subjects to placebo). These subjects will be assigned to 1 of 4 weight groups based on weight at the screening visit: Weight Group 1 [redacted] Weight Group 2 [redacted] Weight Group 3 [redacted] and Weight Group 4 [redacted] Subjects will receive the dose for their assigned weight group at each dose level as indicated in the table below. The titration period will include [redacted] at Dose Level 1, [redacted] at Dose Level 2, [redacted] at Dose Level 3, and [redacted] at Dose Level 4.

Weight Group	Body Weight (kg)	Dose Level 1 (mg) tid	Dose Level 2 (mg) tid	Dose Level 3 (mg) tid	Dose Level 4 (mg) tid
1	[redacted]				
2					
3					
4					

tid = 3 times a day.

After [redacted] of the titration period, the investigator may decrease a subject's dose to the lower tolerated dose level based on safety and tolerability. In addition to the assessment of safety and tolerability at the titration period study visits, the study site will contact the parent/caregiver by telephone call approximately 1 week after the dose titration visits for Dose Levels 3 and 4 (ie, at the end of [redacted]) to assess for any adverse events. Subjects who are unable to escalate to or tolerate Dose Level 2 should be discontinued from study treatment.

Once the Sentinel Cohort titration period has completed, the DMC will review safety, tolerability, and PK data as described in the DMC charter. Upon completion of the review and based on recommendations from the DMC,

subjects may be randomized in the Main Cohort. Doses, weight groups, and dose titration targets in the Main Cohort may be modified based on the results of the Sentinel Cohort safety, tolerability and PK data; however, the average target exposures [redacted]

Titration Period - Main Cohort

Approximately 44 subjects will be randomized into the Main Cohort in a 1:1 ratio (NBI-921352:placebo). Beginning on Day 1, subjects will receive Dose Level 1 for their assigned weight group (based on weight at the screening visit). The titration period will include [redacted] at Dose Level 1, [redacted] at Dose Level 2, [redacted] at Dose Level 3, and [redacted] at Dose Level 4, with subjects receiving the dose for their weight group at each dose level as indicated in the table above, or as determined based on the results of the Sentinel Cohort data review by the DMC.

After [redacted] of the titration period, the investigator may decrease a subject's dose to the lower tolerated dose level based on safety and tolerability. Subjects who are unable to escalate to or tolerate Dose Level 2 should be discontinued from study treatment.

Maintenance Period – Sentinel and Main Cohorts

Subjects in both cohorts who complete the titration period will enter the [redacted] maintenance period. During the maintenance period, subjects will continue to receive their final tolerated dose from the titration period. Dose levels should not be changed during the maintenance period without prior Sponsor approval. Rescue medication is permitted at any time during the study and will not be a reason for discontinuation from study treatment; however, use of rescue medication will be collected in the seizure diary and must be documented in the electronic case report form (eCRF).

Subjects receiving Dose Levels 3 or 4 who discontinue study treatment at any time before the end of Week 16, including during the titration period, should undergo dose de-escalation, if appropriate, during which the subject's current dose will be reduced in a step-wise manner over a period of up to [redacted] Instructions for dose de-escalation will be provided. Subjects who withdraw from the study will not be replaced. Subjects receiving Dose Levels 1 or 2 who discontinue study treatment do not require dose de-escalation.

Following completion of the maintenance period, subjects will have the option to continue in the active extension study if they have successfully completed the 16-week treatment period [redacted] titration and [redacted] maintenance) in the current study AND have not had a serious or severe adverse event (AE) that, in the investigator's opinion, was related to study treatment and would make it unsafe for the subject to continue study treatment dosing. [redacted]

Taper Period

If the subject completes the maintenance period and does not enroll in the active extension study, the subject will enter a [redacted] taper period where the study treatment is tapered to ensure that all subjects will be off study treatment by the end of the [redacted].

Safety Follow-Up Period

After the last dose of study treatment, subjects who do not enroll in the active extension study will enter a [redacted] safety follow-up period which includes a follow-up telephone call approximately 1 week after the last dose of study treatment and a visit approximately [redacted] after the last dose of study treatment.

Study population: A total of approximately 52 male and female subjects, 2 to 21 years of age, with a diagnosis of SCN8A-DEE reviewed and approved by the DCP will be enrolled. [redacted] Enrollment of eligible subjects will not be limited based on weight group or age group.

Duration of treatment and study participation: The expected duration of study participation from screening to last visit for each subject is approximately [redacted] for subjects enrolling in the active extension study and approximately 30 weeks [redacted] plus [redacted] taper and [redacted] safety follow-up period) for subjects who choose not to enroll in the active extension study.

Investigational product, dosage and mode of administration: [redacted]

Reference therapy, dose and mode of administration, batch number: Placebo capsules identical in appearance to the test product will be taken in the same manner and on an identical schedule as NBI-921352.

Criteria for Evaluation:

Efficacy:

Daily seizure diaries (collected at each visit) will be used to determine efficacy. The site will review the daily diaries at each visit to confirm appropriateness of completion and re-instruct the parent/caregiver as necessary. Parent/caregivers will also be instructed to document days without any seizures. In addition, use of rescue medication will also be collected.

Clinical Global Impression of Change (CGIC) and Parent/Caregiver Global Impression of Change (GIC) scales

Clinical Global Impression of Severity (CGIS) and Parent/Caregiver Global Impression of Severity (GIS) scales

[redacted]

Pharmacokinetics:

Blood samples to evaluate plasma concentrations of NBI-921352 and metabolites and concomitant ASMs and evaluated metabolites will be collected throughout the study.

Safety:

Safety and tolerability will be monitored throughout the study and will include the following assessments:

- AEs
- Clinical laboratory tests including hematology, clinical chemistry, and urinalysis
- Vital signs
- Physical examinations, including height/length and weight, Tanner staging (as appropriate based on subject age and stage of puberty), and neurological examination
- 12-lead electrocardiograms
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- [redacted]

Study Endpoints: For the endpoints below, countable motor seizures are defined as GTCS, tonic, atonic or FOS with noticeable motor component. The treatment period is defined as the [redacted] titration period and the [redacted] maintenance period combined.

Primary:

- Percentage change from baseline in 28-day seizure frequency for countable motor seizures during the treatment period of the study.

Key Secondary:

- Treatment response defined as a ≥50% decrease from baseline in 28-day seizure frequency for countable motor seizures during the treatment period of the study.

Other Secondary:

- Percentage change from baseline in 28-day seizure frequency for countable motor seizures, during the [redacted] of the maintenance period.
- Treatment response defined as a ≥25%, ≥75%, or 100% decrease from baseline in 28-day seizure frequency for countable motor seizures during the treatment period of the study.
- Treatment response defined as a ≥25%, ≥50%, ≥75%, or 100% decrease from baseline in 28-day seizure frequency for countable motor seizures during the maintenance period of the study.
- CGIC and Parent/Caregiver GIC at each study visit during the treatment period of the study.
- Change from baseline in CGIS and Parent/Caregiver GIS at each visit during the treatment period of the study.

Pharmacokinetic:

- PK parameters for NBI-921352 and metabolites will be determined by standard noncompartmental methods.
- Plasma concentration data for NBI-921352 [redacted]
- [redacted]

Safety:

- Incidence of AEs and suicidality (as measured by either C-SSRS or clinical report of AEs of suicidality depending on subject's age and developmental level).
- Absolute values and changes from baseline in clinical laboratory test values (hematology and clinical chemistry), vital signs, weight, Tanner stage, and electrocardiogram (ECG) parameters.
- [redacted]

Statistical Methods

The primary endpoint is the percentage change from baseline in 28-day seizure frequency for countable motor seizures during the treatment period. All subjects with any seizure data collected during the treatment period will be included in the primary analysis. Subjects in the Sentinel Cohort may be excluded from the primary analysis if changes to dosing are implemented in the Main Cohort. The null hypothesis is the percentage reduction from baseline in 28-day seizure frequency during the treatment period in subjects treated with NBI-921352 is equal to the reduction in subjects treated with placebo. The null hypothesis of no treatment effect will be tested using a Wilcoxon rank-sum test (2-sided test) at the [redacted] significance level.

The proportion of subjects considered treatment responders, defined as a ≥50% decrease from baseline in 28-day seizure frequency for countable motor seizures during the treatment period, will be summarized by treatment group and analyzed using Fisher's exact test.

Safety data, plasma concentrations, and PK parameters (calculated using noncompartmental methods) will be summarized using descriptive statistics.

2. INTRODUCTION

2.1. Epilepsy and Voltage-Gated Sodium Channel Inhibitors

Epilepsy is one of the most common neurological disorders, affecting approximately 65 million people worldwide (Moshe et al., 2015). It is characterized by abnormal electrical activity in the brain leading to seizures. For epidemiological purposes, the definition requires more than one unprovoked seizure of any type. Patients with epilepsy have an increased mortality risk compared with the general population primarily due to the etiology of the disease. However, in patients with uncontrolled epilepsy, which can include up to 30% of patients who are refractory to conventional treatment (Chen et al., 2018), the greatest seizure-related risk of mortality is due to sudden unexpected death in epilepsy (SUDEP) (Hitiris et al., 2007). Uncontrolled epilepsy poses additional risks to pediatric patients; frequent uncontrolled seizures in young children have been shown to have a detrimental effect on cognitive development beyond that caused by the underlying disease (Encinas et al., 2019; O'Callaghan et al., 2011).

The pathophysiology of most forms of epilepsy remains poorly understood, but it is known that epileptic seizures arise from an excessively synchronous and sustained firing of a group of neurons. Persistent increase in neuronal excitability is common to all epilepsy syndromes. Currently available antiseizure medications (ASMs) are considered to act by inhibition of synaptic vesicle glycoprotein (neurotransmitter release), potentiation of the inhibitory gamma-aminobutyric acid (GABA)ergic neurotransmission, reduction of glutamate-mediated excitatory neurotransmission, or inhibition of voltage-gated sodium or calcium channels. Inhibition of voltage-gated sodium channels (Na_V) is a common mechanism of widely prescribed antiepileptic drugs, including carbamazepine, eslicarbazepine, oxcarbazepine, lacosamide, lamotrigine, phenytoin, rufinamide, and zonisamide. [redacted]

2.2. SCN8A Developmental and Epileptic Encephalopathy

SCN8A developmental and epileptic encephalopathy (SCN8A-DEE) is a rare and severe genetically determined neurologic syndrome characterized by early onset developmental delay, cognitive impairment and intractable seizures for which no approved therapy exists. SCN8A-DEE is caused by de novo missense variants in the SCN8A gene, which encodes the pore-forming alpha subunit of $Na_V1.6$. $Na_V1.6$ is among the most ubiquitous sodium channels in the brain and slight alterations in its kinetics of opening and closing can have profound functional effects (O'Brien and Meisler, 2013). Mutations in SCN8A as a cause of epileptic encephalopathy were first described in 2012 (Veeramah et al., 2012). The vast majority of SCN8A mutations that cause SCN8A-DEE result in $Na_V1.6$ gain of function (GOF) by

producing impaired inactivation or abnormal activation causing increased sodium current. This can lead to neuronal hyperexcitability resulting in epileptic seizures (Gardella et al., 2018; Wagnon et al., 2016). A subset of phenotypically distinct cases have been reported in which patients primarily present with movement disorders, developmental delay, and cognitive impairment, with less prevalent or no seizure symptoms, and these cases are predominately associated with loss-of-function (LOF) SCN8A mutations (Liu et al. 2019; Wagnon et al. 2018; Wagnon et al., 2017; Trudeau et al., 2006).

Early onset seizures, which occur at a median age of 4 months, are a hallmark of SCN8A-DEE (Larsen et al., 2015). Seizures vary in frequency, with some patients with SCN8A-DEE experiencing up to several per day. SCN8A-DEE seizures may be prolonged (eg, more than 20 minutes) and may have autonomic features of apnea, bradycardia or tachycardia, and cyanosis at the onset. The most common seizures are generalized motor seizures, motor and nonmotor focal seizures including focal to bilateral tonic-clonic, spasm-like episodes and erratic myoclonus and are most often poorly controlled (Gardella et al., 2018; Schreiber et al., 2020). While the intellectual impairment may vary as a result of SCN8A mutations, development in most children with SCN8A-DEE is severely delayed. The developmental delays are usually present from birth but may appear or become evident after the onset of severe and frequent seizures. Over 90% of children with SCN8A-DEE are nonverbal. Developmental regression has been reported to occur with seizure onset, or seizure worsening. Half of children with SCN8A-DEE are not ambulatory and may have eventual motor decline. Hypotonia and movement disorders consisting of dystonia, ataxia and choreoathetosis may be present. Gastrointestinal disorders are often present, such as gastric reflux, and oral feeding often poses a risk, therefore half of patients are fed through a gastrostomy tube (Gardella et al., 2018). Death occurs at a high rate in SCN8A-DEE; in a cross-sectional review of 190 patients worldwide, the overall mortality rate was 5.3% (10/190), comparable to other epileptic encephalopathies, with 3 of these 10 attributed to SUDEP (Johannesen et al., 2018). Deaths were frequently preceded by progressive neurologic decline accompanied by increased seizures, including status epilepticus, resulting in deaths mostly due to respiratory distress or pulmonary infections.

The majority of described cases of patients with SCN8A-DEE, due to its onset in infancy, are in children and adolescents. This is presumably due to the relatively recent identification of genetic SCN8A variants linked to the infantile epileptic encephalopathy, which were first described in 2012 (Veeramah et al., 2012). However, patients with SCN8A-DEE ≥18 years of age at the time of initial diagnosis have been identified, who have severe disease including frequent seizures similar to younger patients. Deaths due to SUDEP have also been documented in older adolescent and adult patients (Blanchard et al., 2015; Gardella et al., 2018; Gardella and Moller, 2019). Available information from clinicians treating patients with SCN8A-DEE indicates that young adult SCN8A-DEE patients have a similar disease phenotype compared to younger patients and may continue to be treated by their pediatric epileptologists into early adulthood.

Reduction of seizures associated with SCN8A-DEE is the primary goal of treatment; however, there are currently no therapies indicated to treat SCN8A-DEE. SCN8A-DEE seizures are typically very resistant to ASMs. A global dataset characterizing 22 SCN8A-DEE patients found that only 4 patients had significant seizure reduction with existing treatments (Gardella et al., 2018). [redacted]

[redacted]

2.3. NBI-921352

NBI-921352 is a potent, selective, small molecule inhibitor of $Na_V1.6$ channels. [redacted]

A complete summary of the available clinical and nonclinical data for NBI-921352 is provided in the Investigator's Brochure.

3. OBJECTIVES

The objectives for this study are:

Primary

- To assess the efficacy of NBI-921352 as adjunctive therapy on the frequency of countable motor seizures (defined as generalized tonic-clonic seizure [GTCS], tonic, atonic or focal onset seizures [FOS] with noticeable motor component).

Secondary

- To evaluate the efficacy of NBI-921352 using the Clinical and Parent/Caregiver Global Impression of Change scales and the Clinical and Parent/Caregiver Global Impression of Severity scales.
- To characterize the pharmacokinetics of NBI-921352 and determine the effect of NBI-921352 on plasma levels of concomitant ASMs and evaluated metabolites.
- To evaluate the safety and tolerability of NBI-921352.

Exploratory

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4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2 randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, tolerability, and pharmacokinetics of NBI-921352 as adjunctive therapy in subjects with SCN8A-DEE. Approximately 52 male and female subjects will be randomized for study participation according to the study eligibility criteria. Subjects will be randomized 1:1 (NBI-921352:placebo). This study will enroll subjects 2 to 21 years of age. Enrollment of eligible subjects will not be limited based on weight group or age group.

This study will include 2 separate cohorts:

- Sentinel Cohort: 8 subjects will be randomized into the Sentinel Cohort. These subjects will be considered a sentinel group to evaluate observed pharmacokinetics (PK) relative to predicted exposures as well as safety and tolerability. An external, independent Data Monitoring Committee (DMC) will review the Sentinel Cohort subject safety, tolerability, and PK data through the [redacted] titration period prior to randomization of subjects in the Main Cohort. Preliminary efficacy data will not be assessed as part of the interim Sentinel Cohort data review.
- Main Cohort: Once safety, tolerability, and PK have been assessed in the Sentinel Cohort, subjects will be randomized into the Main Cohort.

For both cohorts, this study will consist of 3 periods (for subjects who enroll in the separate, active extension study) or 5 periods (for subjects who do not enroll in the active extension study):

- An up to [redacted] screening period that includes a baseline period of at least [redacted] to collect baseline daily seizure diary data
  - The baseline period may start once the investigator has confirmed that the parent/caregiver is capable of and comfortable with identifying seizures.
- A [redacted] titration period [redacted] at each of the 2 lowest titration dose levels and [redacted] at each of the 2 highest titration dose levels)
- A [redacted] maintenance period
- A [redacted] taper period (for those subjects not enrolling into the active extension study)
- A [redacted] safety follow-up period (for those subjects not enrolling into the active extension study)

Subjects will be eligible to enter the separate, active extension study if they have successfully completed 16 weeks of treatment [redacted] titration period and [redacted] maintenance period). Subjects in the active extension study will receive active treatment; however, treatment received during Study NBI-921352-DEE2012 will remain blinded until the last subject ends their participation in Study NBI-921352-DEE2012 and the study database is locked.

Screening/Baseline Period – Sentinel and Main Cohorts

After informed consent has been provided by the parent/legal guardian or subject (if appropriate) and the subject has provided assent (if appropriate), subjects will be screened for eligibility to participate in the study. Prior to starting the baseline period, site personnel will review the seizure types with the subjects and parent/caregiver and train them on correct seizure identification with a focus on identification of countable motor seizures (defined as GTCS, tonic, atonic seizure, and FOS with an identifiable motor component) as well as noncountable seizures (eg, myoclonic, epileptic spasms, and absence). [redacted] The investigator will document that training has been completed and the parent/caregiver is capable of and comfortable with identifying seizures before the start of the baseline period. The investigator will also document that the subject has an adequate rescue medication regimen as well as a nocturnal alerting system in place. Baseline daily seizure diary data must be collected for at least [redacted], during which the parent/caregiver will complete the daily diary to record the number and type of countable motor seizures, as well as the occurrence of noncountable seizures for recording of seizure-free days. After completion of the baseline period, final eligibility will be confirmed by the investigator after review of the baseline diary data to ensure that parent/caregivers completed the diary according to instructions and that the subject has sufficient frequency of countable motor seizures (on average at least 1 countable motor seizure per week [4 per 28 day period]).

A sample for comprehensive genetic epilepsy panel testing will be collected at screening and used to verify the diagnosis. The clinical and genetic findings supporting the diagnosis of SCN8A-DEE will be reviewed and confirmed by an external Diagnosis Confirmation Panel (DCP) based on guidelines outlined in the DCP charter.

Rescreening is permitted if a subject does not meet all eligibility requirements and returns to be rescreened. A subject that has failed screening twice may not be rescreened again without prior permission from the Sponsor. Subjects who do not meet seizure frequency criteria as assessed during a completed baseline period will not be eligible for rescreening. Genotyping assessments do not need to be repeated for subjects who are rescreened.

Titration Period - Sentinel Cohort

The first 8 subjects will be randomized into the Sentinel Cohort in a 1:1 ratio (4 subjects to NBI-921352 and 4 subjects to placebo). These subjects will be assigned to 1 of 4 weight groups based on weight at the screening visit: Weight Group 1 [redacted], Weight Group 2 [redacted], Weight Group 3 [redacted] and Weight Group 4 [redacted]. Subjects will receive the dose for their assigned weight group at each dose level as indicated in Table 1. The titration period will include [redacted] at Dose Level 1, [redacted] at Dose Level 2, [redacted] at Dose Level 3, and [redacted] at Dose Level 4.

Table 1: Titration Period Doses by Weight Group

Weight Group	Body Weight (kg)	Dose Level 1 (mg) tid	Dose Level 2 (mg) tid	Dose Level 3 (mg) tid	Dose Level 4 (mg) tid
1	[redacted]				
2					
3					
4					

tid = 3 times a day.

After [redacted] of the titration period, the investigator may decrease a subject's dose to the lower tolerated dose level based on safety and tolerability. In addition to the assessment of safety and tolerability at the titration period study visits, the study site will contact the parent/caregiver by telephone call approximately 1 week after the dose titration visits for Dose Levels 3 and 4 (ie, at the end of [redacted] to assess for any adverse events. Subjects who are unable to escalate to or tolerate Dose Level 2 should be discontinued from study treatment.

Once the Sentinel Cohort titration period has completed, the DMC will review safety, tolerability, and PK data as described in the DMC charter. Upon completion of the review and based on recommendations from the DMC, subjects may be randomized in the Main Cohort. Doses, weight groups, and dose titration targets in the Main Cohort may be modified based on the results of the Sentinel Cohort safety, tolerability and PK data; however, [redacted]

Titration Period - Main Cohort

Approximately 44 subjects will be randomized into the Main Cohort in a 1:1 ratio (NBI-921352:placebo). Beginning on Day 1, subjects will receive Dose Level 1 for their assigned weight group (based on weight at the screening visit). The titration period will include [redacted] at Dose Level 1, [redacted] at Dose Level 2, [redacted] at Dose Level 3, and [redacted] at Dose Level 4, with subjects receiving the dose for their weight group at each dose level as indicated in Table 1, or as determined based on the results of the Sentinel Cohort data review by the DMC.

After [redacted] of the titration period, the investigator may decrease a subject's dose to the lower tolerated dose level based on safety and tolerability. Subjects who are unable to escalate to or tolerate Dose Level 2 should be discontinued from study treatment.

Maintenance Period – Sentinel and Main Cohorts

Subjects in both cohorts who complete the titration period will enter the [redacted] maintenance period. During the maintenance period, subjects will continue to receive their final tolerated dose from the titration period. Dose levels should not be changed during the maintenance period without prior Sponsor approval. Rescue medication is permitted at any time during the study and will not be a reason for discontinuation from study treatment; however, use of rescue medication will be collected in the seizure diary and must be documented in the electronic case report form (eCRF).

Subjects receiving Dose Levels 3 or 4 who discontinue study treatment at any time before the end of Week 16, including during the titration period, should undergo dose de-escalation if appropriate, during which the subject's current dose will be reduced in a step-wise manner over a period of up to [redacted]. Instructions for dose de-escalation will be provided. Subjects who withdraw from the study will not be replaced. Subjects receiving Dose Levels 1 or 2 who discontinue study treatment do not require dose de-escalation.

Following completion of the maintenance period, subjects will have the option to continue in the active extension study if they have successfully completed the 16 week treatment period [redacted] titration and [redacted] maintenance) in the current study AND have not had a serious or severe adverse event (AE) that, in the investigator's opinion, was related to study treatment and would make it unsafe for the subject to continue study treatment dosing. For subjects electing to enroll in the active extension study, the last study visit will occur at the end of the maintenance period, and the first visit of the active extension study will occur at the same visit.

Taper Period

If the subject completes the maintenance period and does not enroll in the active extension study, the subject will enter a [redacted] taper period where the study treatment is tapered to ensure that all subjects will be off study treatment by the end of the [redacted] The dose taper procedure is described in Section 9.5.3.

Safety Follow-Up Period

After the last dose of study treatment, subjects who do not enroll in the active extension study will enter a [redacted] safety follow-up period which includes a follow-up telephone call approximately 1 week after the last dose of study treatment and a visit approximately [redacted] after the last dose of study treatment.

A schematic of the study design is shown in Figure 1.

Figure 1: [redacted]

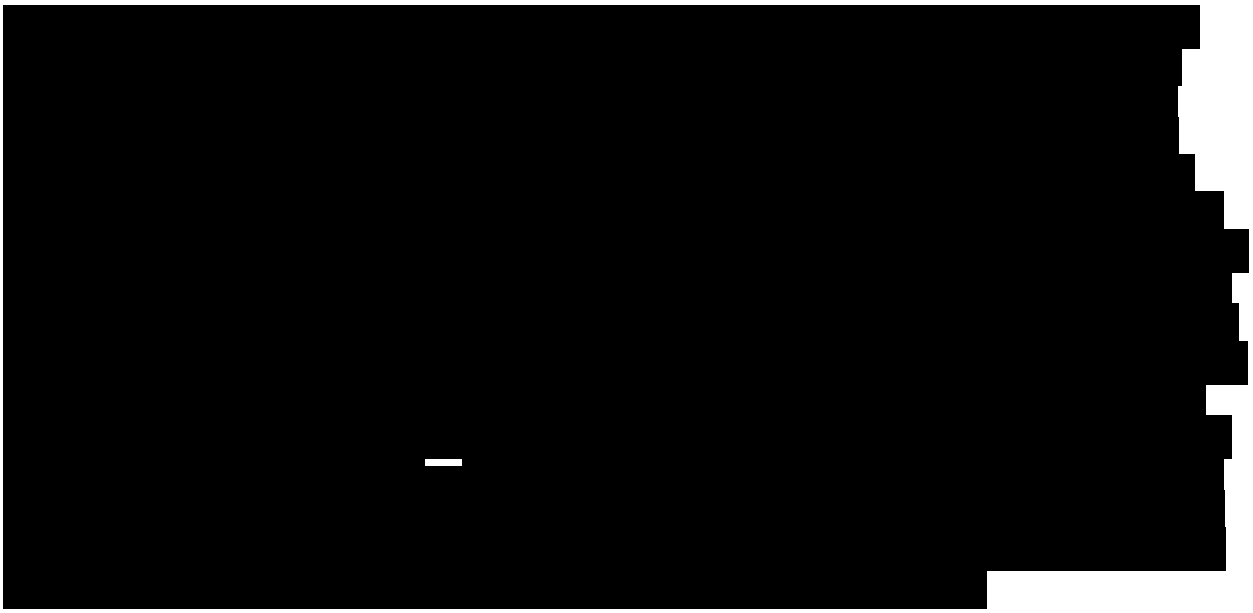
4.2. Study and Dose Rationale

This Phase 2 randomized, double-blind, placebo-controlled study is designed to evaluate the efficacy, safety, tolerability, and PK of NBI-921352 doses administered tid as adjunctive therapy in subjects 2 to 21 years of age with SCN8A-DEE.

The titration doses and weight groups selected for this study were identified using simulations based on a population PK model developed with data from the 2 NBI-921352 Phase 1 healthy adult studies. The NBI-921352 titration doses used in this study are predicted to provide the specified target average maximum plasma concentration for each dose level based on weight group (Table 2).

Table 2: [redacted]

[redacted]



After [redacted] PK data will be assessed in the Sentinel Cohort, doses, dose titration targets, and/or weight groups for the Main Cohort may be adjusted; however, [redacted]

4.3. Study Duration

The expected duration of study participation from screening to last visit for each subject is approximately [redacted] for subjects enrolling in the separate active extension study and approximately 30 weeks ([redacted] plus [redacted] taper and [redacted] safety follow-up period) for subjects who choose not to enroll in the active extension study.

4.4. End of Study Definition

The end of the study is defined as the date of the last study visit of the last subject in the study.

4.5. Benefit-Risk Assessment

SCN8A-DEE is a severe and rare neurologic syndrome caused by de novo missense variants in the SCN8A gene, which encodes the pore-forming alpha subunit of $Na_V1.6$. Currently no therapies are indicated to treat SCN8A-DEE, and seizures in SCN8A-DEE patients are typically very resistant to existing ASMs. SCN8A-DEE patients are at risk for developmental delay, cognitive impairment, and life-threatening status epilepticus and SUDEP, and the lack of an effective therapy for these patients establishes a clear unmet medical need.

NBI-921352 is a potent, selective, small molecule inhibitor of $Na_V1.6$ channels. [redacted]

channels and the selectivity of NBI-921352 for Na$_V$1.6 against other human Na$_V$ isoforms.

[redacted]

The DMC will monitor safety and tolerability data throughout the study. The current study includes a Sentinel Cohort of 8 subjects (4 NBI-921352 and 4 placebo). Once the Sentinel Cohort has completed the [redacted] titration period, an external, independent DMC will review safety, tolerability, and PK data before subjects are randomized in the Main Cohort. Based on the DMC review of the Sentinel Cohort data, the doses, weight groups, and dose titration targets in the Main Cohort may be modified but [redacted]

ASMs as a class are associated with potential risks, including cardiovascular effects, CNS effects including increased risk of seizures, an increased risk of suicidal thoughts or behavior, and hypersensitivity reactions. The current study includes vital signs assessments and centrally read 12-lead ECGs throughout the study to monitor for cardiovascular abnormalities, and subjects with clinically significant abnormal ECG findings or vital signs at screening will be excluded from the study. [redacted] Safety and tolerability will be assessed at each dose level by the investigator before a subject's dose is increased to the next dose level. Subjects who are unable to tolerate Dose Levels 1 or 2 for their weight group will be discontinued from study treatment. Beginning at [redacted] of the titration period, doses may be decreased to a lower, tolerated dose level based on safety and tolerability. Study procedures are in place to ensure that subjects are monitored appropriately for seizure

exacerbations. Treatment regimens and prevention strategies are included to address serious events, such as status epilepticus and nocturnal seizures, which may result in SUDEP.

Other CNS adverse events will also be monitored during the study. Suicidality will be monitored using the C-SSRS or clinical impression for subjects for whom the C-SSRS would be inappropriate due to developmental reasons. [redacted]

SCN8A-DEE is associated with increased risk of life-threatening conditions, including status epilepticus and SUDEP (Johannesen et al., 2018); these conditions represent potential risks for all subjects in the proposed Phase 2 Study NBI-921352-DEE2012 and the risk of developing these conditions may be higher for subjects who are randomized into the placebo treatment group. However, all subjects must be receiving concomitant ASM therapy, including a requirement for an established regimen for rescue-medication administration, and treatment with up to 4 ASMs is allowed during the study. Subjects in both treatment groups in Study NBI-921352-DEE2012 who complete the 16-week treatment period may be eligible to receive NBI-921352 in the separate, active extension study [redacted]

5. STUDY POPULATION

Subjects must fulfill all inclusion and exclusion criteria to participate in the study.

5.1. Inclusion Criteria

Subjects must meet all of the following inclusion criteria:

1. Written or oral pediatric assent from the subject if deemed capable of providing assent, and written informed consent from the subject's parent(s) or legal guardian(s) for subjects <18 years of age and for subjects ≥18 years of age who are not capable of providing consent in accordance with the governing Independent Ethics Committees (IEC)/Institutional Review Boards (IRB) and according to local laws and regulations. Subjects who are ≥18 years of age and capable of providing consent should sign an Informed Consent Form (ICF). Informed consent/assent may be done remotely, if allowed and remote consenting procedures are in place.
2. Be a male or female 2 to 21 years of age, inclusive.
3. Have a diagnosis of SCN8A-DEE supported by both clinical and genetic findings outlined as follows:
    a. Clinical findings:
        i. Required
            1. Seizure onset prior to 18 months of age
            2. Developmental delay which may have occurred either prior to or with onset of seizures or after
        ii. Supportive (not required):
            1. Multiple seizure types which include focal seizures (including focal to bilateral tonic-clonic), tonic-clonic seizures, epileptic/infantile spasms, tonic seizures
            2. History or ongoing motor abnormalities including hypotonia, dystonia, choreoathetosis, ataxia, spasticity, hyperekplexia
            3. Episodes of convulsive and nonconvulsive status epilepticus
            4. Beneficial response to sodium channel blockers such as phenytoin, valproate, carbamazepine, lacosamide, lamotrigine, rufinamide, and oxcarbazepine
    b. Genetic findings (i, ii, and iii required):
        i. Pathological gain of function (GOF) mutation in SCN8A defined as either a previously identified GOF mutation or a presumed pathological GOF mutation. Presumed pathological GOF mutations must be either a missense mutation that is not seen in either parent (de novo) OR a mutation which leads to a hyperfunctioning channel in in vitro function tests. Presumed pathological GOF mutations must not be nonsense mutations or other mutations likely to lead to a truncated protein.
        ii. Subject may not have an identified (known or newly functionally characterized missense variant) or presumed (ie, protein-truncating variant) loss-of-function variant in SCN8A.

iii. No other pathogenic mutation in an additional gene that is known to cause epilepsy and is more likely to cause the epilepsy experienced by the subject.

Genetic findings required for SCN8A-DEE diagnosis may be based on genetic testing performed previously. The genetic mutation in the subject's SCN8A gene (b[i] and b[ii]) and the absence of other pathogenic mutations that are more likely to cause the epilepsy experienced by the subject (b[iii]) must be confirmed at screening as part of the comprehensive epilepsy panel genotyping (Section 9.1.1).

4. Have SCN8A-DEE diagnosis confirmed by the DCP.
5. In the 90 days before screening, have a history of on average at least 4 countable motor seizures (defined as GTCS, tonic, atonic or FOS with noticeable motor component) per month.
6. Have on average at least 1 countable motor seizure (defined as GTCS, tonic, atonic or FOS with noticeable motor component) per week (4 per 28-day period) and not be seizure-free for more than 20 consecutive days per 28-day period during the baseline period.
7. Have at least [redacted] of reliably and consistently completed baseline seizure diary data.
8. Being treated with at least 1 other ASM, but no more than 4 ASMs. Epidiolex®/Epidyolex® will be considered an ASM. The dose should be stable for at least 5 half-lives at screening. Vagus nerve stimulator (VNS) and ketogenic diet are not counted as ASMs.
9. Have failed to achieve seizure freedom with at least 2 ASMs.
10. The subject, if using a VNS, must have had the VNS placed at least 3 months prior to screening with stable settings for ≥30 days before screening; settings must remain stable throughout the duration of the study.
11. The subject, if on a ketogenic diet, must have started the ketogenic diet at least 30 days prior to screening; diet must be stable, and continue through the duration of the study.
12. Must be using a nocturnal alerting system or practice consistent with standards of care at the time of screening and continue to use this for the duration of the study. Acceptable nocturnal alerting systems or practices include but are not limited to:
    - [redacted]
    - [redacted]
    - [redacted]
13. Must have an adequate rescue medication regimen per the investigator's judgment in place at the time of screening and for the duration of the study.
14. Female subjects of childbearing potential must agree to use contraception consistently from screening until the final study visit or 30 days after the last dose of study treatment, whichever is longer.

A female subject of childbearing potential is defined as [redacted] A male subject of childbearing potential is defined as a [redacted].

Highly effective methods of contraception are required for female subjects of childbearing potential:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Male subjects must agree to use effective barrier contraception consistently from screening until 30 days after the last dose of study treatment. The acceptable method of contraception for male subjects, [redacted]

15. Have a body weight of [redacted]
16. Be able to carry out all the appropriate assessments and take the study treatment with the help of the parent/caregiver in the opinion of the investigator.
17. The subject's parent/caregiver is able to accurately identify seizure types, especially countable motor seizures [redacted] and is able to complete seizure diary.

5.2. Exclusion Criteria

Subjects will be excluded from the study if they meet any of the following criteria:

1. Have previously been enrolled in this study and received blinded treatment.
2. Have participated in an interventional clinical trial <30 days prior to screening.
3. Have symptoms that would be more consistent with another epilepsy disorder such as Dravet syndrome (eg, fever-induced episodes of status epilepticus, frequent myoclonic seizures, worsening on sodium channel blockers, absence seizures with generalized spike-and-wave EEG as the sole seizure type).
4. Are currently receiving cannabinoids or medical marijuana except Epidiolex/Epidyolex, unless approved by the Sponsor.
5. Are currently taking systemic steroids (excluding inhaled medication for asthma treatments and intranasal steroids for allergies) such as adrenocorticotropin hormone (ACTH), high dose prednisolone for epileptic spasms. If subject has received these medications in the past, must be off these medications for at least 3 months prior to the screening visit and these drugs may not be initiated during the duration of the study. Intermittent steroids to treat nonepilepsy related diseases (such as allergies or dermatological conditions) are not exclusionary.
6. [redacted]
7. Have a history of severe drug allergy or hypersensitivity to NBI-921352 or its excipients.
8. Have a previous exposure to NBI-921352.
9. Have any other disorder for which the treatment takes priority over treatment of SCN8A-DEE or is likely to interfere with study treatment or impair treatment compliance.
10. Have a history of moderate or severe head trauma or other neurological disorders or systemic medical diseases that are, in the investigator's opinion, likely to affect nervous system functioning.
11. Have a clinically significant medical condition or chronic disease (including history of neurological, hepatic, renal, cardiovascular, gastrointestinal, significant malabsorption, hematologic, pulmonary, psychiatric, or endocrine disease) that in the opinion of the investigator would preclude the subject from participating in and completing the study or that could confound interpretation of study outcome.
12. Are taking or have received disallowed concomitant medication (Section 7.1) or it is anticipated that the subject will require treatment with at least one of the disallowed concomitant medications during the study.
13. Have clinically significant abnormal vital signs at the screening visit as determined by the investigator.

14. Have one or more clinical laboratory test values outside the reference range, based on blood samples taken at the screening visit, that are of potential risk to the subject's safety as determined by the investigator, or have at the screening visit:
    - A serum creatine value >1.5 times the upper limit of the reference range.
    - A total bilirubin value >1.5 times the upper limit of the reference range.
    - A serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) value >2.5 times the upper limit of the reference range. For subjects on valproate, ALT or AST values up to 3 times the upper limit of the reference range are acceptable, if these values have remained stable over the past 3 months based on investigator judgement.
15. Have, at the screening visit, an ECG finding of a corrected QT interval using Fridericia's formula (QTcF) >450 msec or presence of any significant cardiac abnormality.
16. The subject or subject's parent/caregiver, in the investigator's opinion, is unlikely to comply with the protocol, including the requirement to travel to the study sites for study visits, or is unsuitable for any reason.
17. Have attempted suicide within the last year or are at significant risk of suicide (either in the opinion of the investigator or defined as a "yes" to suicidal ideation questions 4 or 5 or "yes" to suicidal behavior on the C-SSRS within the past 12-months).
18. Females who are pregnant or currently breastfeeding.
19. Have a history of a positive hepatitis A virus immunoglobulin M (HAV-IgM), hepatitis B surface antigen (HBsAg), or human immunodeficiency virus antibody (HIV-Ab) test results at screening. Subject with positive hepatitis C antibody (HCV-Ab) and confirmatory positive polymerase chain reaction (PCR) reflex test results at screening will be allowed to participate in the study provided that the subject is asymptomatic as assessed by the investigator and does not have exclusionary liver function test abnormalities (ALT, AST, and total bilirubin).
20. [redacted]

6. STUDY TREATMENT

6.1. General Information

Study treatments are summarized in Table 3.

Table 3: Study Treatments

Group Name	NBI-921352	Placebo
Doses	Subjects will receive up to 4 dose levels during the study based on their assigned weight group. [redacted]	Placebo is administered in the same manner and on an identical schedule as NBI-921352.
Unit Dose Strengths	[redacted]	Placebo
Dose Formulation	[redacted]	Matching oral granules in sprinkle capsules
Route of Administration	Oral or G-tube	Oral or G-tube
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labeling	Study treatment will be provided [redacted]	Matching placebo will be provided [redacted]

tid=3 times a day; WG=weight group.

6.2. Study Treatment Administration

[redacted]

6.3. Study Treatment Storage and Compliance

The designated personnel is responsible for maintaining records of the quantity and dates of all study treatment supplies received, dispensed, returned, lost, and destroyed, according to applicable regulations and study procedures. Study treatment should be stored in a locked area accessible only to the designated pharmacist or qualified personnel. A detailed description of how study treatment should be dispensed, stored, and reconstituted, and any stability changes will be provided in the Pharmacy Manual.

6.4. Study Treatment Accountability and Return

Parents/caregivers will bring all unused study treatment and empty packaging material to the center at specified study visits for drug accountability and reconciliation by study center personnel. A compliance check will be performed by counting the capsules returned at each study visit.

The quantity of study treatment dispensed, used, and returned will be recorded on a dispensing log or otherwise documented. The quantity of study treatment lost or destroyed must also be accounted for and documented. The designated pharmacist or qualified personnel will be responsible for maintaining accurate records of the quantity and dates of all study treatment supplies received, dispensed, and returned.

Returns will be shipped to NBI or its designee at the completion of the study according to instructions provided by NBI or its designee according to applicable local and national regulations and study procedures.

6.5. Direct-to-Subject Shipments of Study Treatment

To ensure continued access to study treatment, if a subject is unable to go to the site when study treatment is to be dispensed, study treatment may be delivered from the site's pharmacy to the subject's residence by a distributor independent from the Sponsor. The subject's name, address, and other contact details will not be accessible to the Sponsor, and the distributor will not have access to the subject's health information.

6.6. Blinding

This is a double-blind, placebo-controlled study during which the subject, parent/caregivers, investigator, all study center personnel, and the Sponsor, with the exception of clinical trial material supply chain personnel who do not have access to study data and are not involved in decisions regarding subject's treatment, will be blinded to the subject's treatment assignment (NBI-921352 or placebo).

The randomization code will be broken for an individual subject only if the subject is pregnant, experiences a serious adverse event (SAE) that the investigator feels cannot be adequately treated without knowing the subject's treatment assignment, or for regulatory reporting requirements. In the case of a medical emergency in which knowledge of the identity of the study treatment is important for subject management, the investigator has the responsibility to decide whether to break the blind; treatment assignments will be unblinded following the interactive web response system (IWRS) process. It is recommended that the investigator contact

the Study Medical Monitor (or designee) before unblinding the treatment assignment if it would not result in unnecessary delay to the immediate medical management of the subject. The investigator must document the date, time, and the reason the blind was broken.

Members of the DMC, the independent statistics group that generates the DMC reports, and the pharmacokineticist providing the PK analysis for the Sentinel Cohort will be unblinded throughout the study.

6.7. Procedures for Overdose

For this study, any dose of NBI-921352 greater than the subject's assigned dose level within a 24-hour time period will be considered an overdose. The current version of the Investigator's Brochure should be referenced for overdose information. There is no recommended specific treatment for an overdose but to provide supportive care if clinically indicated.

In the event of a suspected overdose, the investigator and/or treating physician should:

1. Closely monitor the subject for any AE/SAE and laboratory abnormalities and follow the AE reporting process. The Study Medical Monitor should be contacted for adverse events related to an overdose.
2. Document the quantity of the excess dose(s), as well as the date(s) on which the additional dose(s) were taken, if this information is available.

Subjects who overdose will be counseled on correct dosing and administration of study treatment. Decisions regarding study discontinuation, dose interruptions, or dose modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

7. SUBJECT RESTRICTIONS

7.1. Prior and Concomitant Medications

All prescription and over-the-counter medications, dietary supplements (including vitamins), and herbal supplements taken by the subject within 30 days before screening will be recorded on the Prior and Concomitant Medications page of the eCRF. All previously taken ASMs and reasons for discontinuation will also be recorded on a separate eCRF.

The following medications are prohibited for all subjects beginning 30 days before the screening visit (unless otherwise stated) until the final study visit (or upon early discontinuation of study treatment):

- Cannabinoids or medical marijuana except Epidiolex/Epidyolex, unless approved by the Sponsor.
- Systemic steroids (eg, high dose prednisolone, ACTH) are prohibited for at least 3 months before the screening visit. Inhaled steroids for asthma treatments and intermittent steroids to treat nonepilepsy related diseases (such as allergies or dermatological conditions) are allowed.

- Any investigational treatments received in the context of a clinical study, unless approved by Sponsor.

[redacted]

ASMs must be stable throughout the study.

Rescue Medication

Subjects must have an adequate rescue medication regimen in place for the duration of the study. Short-term benzodiazepines may be used as acute treatment for prolonged seizures. If needed, longer-acting ASMs may be used as rescue medication based on the investigator's discretion. Rescue medication is permitted at any time and will not be a reason for discontinuation from study treatment; however, use of rescue medication will be collected in the seizure diary and must be documented in the eCRF.

7.2. Dietary and Other Restrictions

[redacted]

Subjects who are on a ketogenic diet must have started the diet at least 30 days prior to screening and diet must remain stable throughout the study. If using VNS, subjects must have stable settings for at least 30 days before screening and throughout the study.

[redacted]

8. DISCONTINUATION OF STUDY TREATMENT AND SUBJECT WITHDRAWAL

Subjects can discontinue study treatment or withdraw their consent to participate in the study at any time. The investigator must discontinue study treatment dosing or withdraw any subject from the study at the parent/caregiver or subject's request. All subjects discontinuing study treatment dosing should continue study participation for safety and efficacy assessments through the end of Week 16, after which they will be withdrawn.

8.1. Discontinuation of Study Treatment

If a subject prematurely discontinues study treatment dosing, the investigator will record the reason for discontinuation on the relevant eCRF. Such subjects will not be automatically withdrawn from the study and should continue participation. Data for any outcome measures, particularly the primary and secondary endpoints, as well as safety follow-up, are important to collect. PK sampling is not required after study treatment has been discontinued; however,

subjects should return to the study center at the next scheduled visit for safety assessments. Additional study visits and assessments for subjects who discontinue study treatment but agree to remain in the study may be conducted remotely. Medications listed in Section 7.1 are no longer prohibited after study treatment discontinuation.

Reasons for discontinuation from study treatment include but are not limited to:

- Withdrawal by subject
- Death
- Lost to follow-up
- Site termination by the Sponsor
- Study termination by the Sponsor
- AE
- Pregnancy
- Lack of efficacy
- Protocol deviation

The investigator must discontinue study treatment dosing if the subject experiences any of the following:

- If the type, frequency, or severity of any AE becomes unacceptable/intolerable. This includes AEs of seizures. Criteria for evaluating whether seizures should be considered AEs are provided in Section 10.1.
- A clinically significant worsening in the underlying seizure disorder requiring an adjustment in concomitant ASM regimen to ensure subject safety, including increased usage of rescue medication.
- If the subject is unable to tolerate Dose Levels 1 or 2 for the assigned weight group.
- QTcF of >500 msec (cardiologist verified) on any ECG tracing.
- QTcF change from baseline >60 msec (cardiologist verified) and confirmed with repeated ECG measure.
- If the subject exhibits suicidal behavior, or suicidal ideation of type 4 (active suicidal ideation with some intent to act, without specific plan) or type 5 (active suicidal ideation with specific plan and intent) based on the C-SSRS.
- If the subject is confirmed to be pregnant.
- Withdrawal of consent/assent for study treatment administration by parent/caregiver or subject.

It is crucial to obtain follow-up data for any subject who discontinues study treatment dosing because of an AE, abnormal laboratory test, vital sign measurement, physical examination, or ECG finding. In any case, every effort must be made to undertake safety follow-up procedures.

8.2. Withdrawal from Study

If a subject prematurely withdraws from the study, the investigator will record the reason for withdrawal on the relevant eCRF. All subjects who withdraw from the study prematurely will be asked to have all early termination assessments performed and, unless consent has been withdrawn, will be asked to come back approximately [redacted] later for a follow-up visit. If a subject's last dose of study treatment was [redacted] before the early termination visit, no additional visits are needed.

Reasons for withdrawal from study include but are not limited to:

- Withdrawal by the subject or parent/caregiver
- AE
- Death
- Lost to follow-up
- Site terminated by Sponsor
- Study terminated by Sponsor
- Protocol deviation
- Investigator decision

8.3. Sponsor's Termination or Suspension of Study or Study Site

The Sponsor or designee reserves the right to close a study site, terminate the study, or suspend the study overall or at the level of individual sites at any time for any reason at the sole discretion of the Sponsor. Reasons for terminating the study include, but are not limited to, a determination of unjustifiable risk or toxicity in the risk-benefit assessment based on the occurrence of adverse events or other safety findings that, in their nature, severity, duration, or frequency, require re-evaluation of the current established safety profile, or new scientific evidence (eg, results from other clinical studies) becomes available that may affect subject safety. If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs), the regulatory authorities, and any contract research organizations (CROs) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

9. STUDY ASSESSMENTS AND PROCEDURES

A schedule of assessments is shown in Table 10 in Appendix A. No study procedures should be performed until after signed informed consent by parent(s) or legal representative(s) and, if applicable, informed consent for subjects ≥18 years of age or pediatric assent from subjects <18 years of age determined by the investigator to be capable of providing consent/assent, are obtained. Informed consent/assent may be done remotely, if allowed and remote consenting

procedures are in place. Subject-related events and activities including specific instructions, procedures, concomitant medications, dispensing of study treatment, and descriptions of AEs should be recorded in the appropriate source documents and eCRFs.

The sponsor will store biosamples and the results of any genetic testing in a manner compliant with applicable national and local regulations and the requirements of Articles 25, 26, 28, and 32 of the European Union (EU) General Data Protection Regulation (GDPR).

9.1. Screening Assessments

9.1.1. Comprehensive Epilepsy Panel Genotyping

[redacted]

9.1.2. Cytochrome P450 2D6 Genotyping

[redacted]

9.1.3. Video Electroencephalogram

A video-EEG may be performed during screening at the discretion of the investigator, if a recent (within 3 years) video-EEG is not available and the subject and parent(s)/legal representative(s) provide consent/assent. The video-EEG is optional and will be used for parent/caregiver training in the detection and classification of countable seizures. The video-EEG will be obtained using the standard procedures for the study center.

9.1.4. Diagnosis Confirmation Panel

An external DCP, consisting of clinical and research experts in pediatric epilepsy and SCN8A, will review and confirm that the subject meets the clinical and genetic diagnosis of SCN8A-DEE to determine study eligibility. The DCP will be provided the results of the comprehensive epilepsy panel genotyping during screening to review in order to confirm the genetic diagnosis. Medical history information, as well as any further medical information supporting the diagnosis if available, will be provided to the DCP for review to confirm that the subject meets the clinical diagnosis of SCN8A-DEE. DCP confirmation of the clinical and genetic diagnosis of SCN8A-DEE must be provided before subject randomization. A DCP charter will describe the responsibilities, data review procedures, and diagnostic guidelines for the members to follow.

9.2. Efficacy Assessments

9.2.1. Daily Seizure Diary

Seizure information will be recorded in a paper daily diary throughout the study. The parent/caregiver will complete the daily diary to record the number and type of countable motor seizures [redacted] as well as the occurrence of noncountable seizures [redacted] for recording of seizure-free days. Parent/Caregivers will also be instructed to document days without any seizures and rescue medication use in the daily diary.

Parent/caregivers will be instructed to bring the completed daily seizure diary to each study visit as noted in the Schedule of Assessments (Table 10). At the Day 1 visit prior to randomization, the study center will review the daily seizure diary to confirm that there are at least 4 weeks (28 days) of reliably and consistently completed baseline seizure diary data. At subsequent study visits, the study center will review the daily seizure diary to confirm appropriateness of completion and re-instruct the parent/caregiver as necessary.

9.2.2. Clinical Global Impression of Change

The Clinical Global Impression of Change (CGIC), which is based on a 7-point scale (range: 1=very much improved to 7=very much worse), will be used to rate the overall global improvement since the initiation of study treatment dosing. This scale is a modification of a scale developed by the Psychopharmacology Research Branch of the National Institute of Mental Health to rate the subject's overall improvement in clinical disorder and provides a global evaluation of improvement over time from the clinician's perspective (Guy, 1976).

The investigator (or qualified designee) will rate the scale at the scheduled timepoints as indicated in the Schedule of Assessments (Table 10); if possible, the same person should rate the CGIC at all timepoints.

9.2.3. Parent/Caregiver Global Impression of Change

The Parent/Caregiver Global Impression of Change (GIC) will be used to assess the parent/caregiver's impression of change in the subject's overall condition since starting study treatment and is rated on a 7-point scale (1=very much improved to 7=very much worse).

The main caregiver will rate the scale at the study visits indicated in the Schedule of Assessments (Table 10). If the main caregiver is not available at the visit where the scale is collected, this information may be captured over the telephone on the day of the visit or within 3 days.

9.2.4. Clinical Global Impression of Severity

The Clinical Global Impression of Severity (CGIS) scale will be used to assess overall severity on a 7-point scale (range: 1=normal, not at all ill to 7=among the most extremely ill patients). The CGIS will be assessed by the investigator (or qualified designee) at the scheduled timepoints as indicated in the Schedule of Assessments (Table 10).

9.2.5. Parent/Caregiver Global Impression of Severity

The Parent/Caregiver Global Impression of Severity (GIS) scale will be used to assess overall severity on a 5-point scale (range: 1=none to 5=very severe).

The main caregiver will rate the scale at the study visits indicated in the Schedule of Assessments (Table 10). If the main caregiver is not available at the visit where the scale is collected, this information may be captured over the telephone on the day of the visit or within 3 days.

9.2.6. [redacted]

[redacted]

9.2.7. [redacted]

[redacted]

9.2.8. [redacted]

[redacted]

9.3. Safety Assessments

Concomitant medication use and AEs will be monitored throughout the study as described in Section 7.1 and Section 10, respectively. Additional safety assessments are described in the following sections.

For any abnormal safety assessment deemed clinically significant, the investigator will perform appropriate follow-up assessments (eg, repeat analysis), until the cause of the abnormality is determined and/or until the value returns to baseline (or within normal limits), or the investigator deems the abnormality to be of no clinical significance.

Appropriate psychiatric evaluation and intervention will be provided for any treatment-emergent suicidal behavior or clinically significant suicidal ideation.

9.3.1. Vital Sign Measurements

Vital sign measurements, including orthostatic systolic and diastolic blood pressure, orthostatic pulse rate, respiratory rate, and body temperature will be measured. Orthostatic blood pressures may be considered optional if the subject is unable to stand (eg, subject is in a wheelchair). If the investigator is unable to obtain orthostatic blood pressures, the reason for noncollection must be captured in the eCRF. Blood pressure and pulse rate will be measured after the subject has been supine for at least 5 minutes and after approximately 2 minutes standing, if possible. Body temperature may be measured orally or at the forehead, ear, or rectum.

Vital sign measurements will be obtained before any scheduled blood sample collection at screening and then at the timepoints specified in the Schedule of Assessments (Table 10).

9.3.2. Medical History

A medical history, including family medical history and social, psychiatric, developmental, and neurological histories, will be taken at the screening visit and updated as needed throughout the study.

9.3.3. Physical and Neurological Examination Including Height/Length and Tanner Staging

The complete physical examination will consist of an assessment of general appearance, skin and mucosae, head, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest/lungs, cardiovascular, abdomen, extremities, musculoskeletal, genito-urinary, and neurological system, including assessment of level of consciousness, mental status, muscle strength and tone, coordination and gait. Height/length will be measured at the screening visit only and may be optional if the subject is unable to stand. If the investigator is unable to obtain height/length, the reason for noncollection must be captured in the eCRF. The complete physical examination will be performed at the study visits indicated in the Schedule of Assessments (Table 10).

Physical signs of puberty will be assessed using Tanner staging in subjects (as appropriate based on subject age and stage of puberty) as part of the physical examination at screening and at the end of maintenance/early termination visit.

9.3.4. Weight

Weight will also be measured at the study visits indicated in the Schedule of Assessments (Table 10). Weight at the screening visit will be used for weight group assignment for study treatment dosing.

9.3.5. Electrocardiogram

A standard 12-lead ECG will be recorded after the subject has rested supine for at least 5 minutes. The ECG will be centrally read and parameters that will be assessed include heart rate, PR interval, QRS duration, QT interval, and QTcF. Additionally, the occurrence of de- and re-polarization and rhythm disorders or other abnormalities will be assessed. Based on the review of these parameters, the investigator will note if the ECG is Normal, Abnormal not Clinically Significant, or Abnormal Clinically Significant. If the ECG is Abnormal Clinically Significant, the investigator or designee will provide a description of the abnormality recorded on the AE eCRF.

9.3.6. Clinical Laboratory Assessments

All clinical laboratory assessments will be performed by a central laboratory. The central laboratory will provide instructions and supplies to the study staff before study initiation and instructions will be included in a laboratory manual. The laboratory test battery will include routine and screening laboratory tests.

The following clinical safety laboratory assays will be performed:

Hematology: [redacted]

Clinical chemistry: [redacted]

Urinalysis: [redacted]

The following additional laboratory tests will be performed:

Serology: [redacted]

Drug screen: [redacted]

Pregnancy test: Pregnancy tests will be performed for female subjects of childbearing potential. A serum (β-hCG) pregnancy test will be performed at the visits indicated in the Schedule of Assessments (Table 10). A urine pregnancy test should be performed at Day 1; however, a serum pregnancy test may be performed, if it is not possible to obtain urine.

The maximum total blood volume collected during the study from screening to last visit in this study [redacted]; Safety Follow-up Visit) is [redacted]

9.3.7. Columbia-Suicide Severity Rating Scale

The C-SSRS is a validated instrument to prospectively assess suicidal ideation and behavior (http://www.cssrs.columbia.edu). There are versions of the questionnaire designed for use at screening (Baseline/Screening version) and at visits throughout the study (Since Last Contact version). All versions of the C-SSRS include a series of screening questions related to suicidal ideation and suicidal behavior. Subject responses of "yes" to one or more screening questions will prompt additional questions that evaluate frequency and intensity of suicidal ideation and/or behavior.

The C-SSRS Baseline/Screening version will be administered at screening. Subjects with developmental impairment for whom the C-SSRS would be inappropriate will be monitored for suicidality based on clinical impression.

Subjects with any suicidal behavior or suicidal ideation of type 4 (active suicidal ideation with some intent to act, without specific plan) or type 5 (active suicidal ideation with specific plan and intent) within the last year based on the C-SSRS should be excluded (refer to exclusion criterion #17 in Section 5.2).

The C-SSRS will be administered and scored by the investigator or qualified study center personnel at screening and throughout the study as indicated in the Schedule of Assessments (Table 10).

9.3.8. [redacted]

9.4. Pharmacokinetic Assessments

Blood samples for determination of plasma concentrations of NBI-921352 [redacted] will be collected. [redacted]. An intravenous catheter inserted in a peripheral vein may be used to collect serial PK blood samples. Timepoints for both blood samples are provided in the Schedule of Assessments (Table 10).

For each sample, blood [redacted] will be collected [redacted] The exact time of sampling in hours and minutes will be recorded for all plasma PK samples. A PK sample should be collected from subjects who terminate early. The blood samples will be processed and stored

according to the procedure as specified in the laboratory manual. Samples will be shipped on dry ice to the central laboratory for analysis.

9.5. [redacted]

9.5.1. [redacted]

9.5.2. [redacted]

9.5.2.1. [redacted]

9.5.2.1.1. [redacted]

[redacted]

9.5.2.1.2. [redacted]

[redacted]

9.5.2.1.3. [redacted]

[redacted]

9.5.2.1.4. [redacted]

[redacted]

9.5.2.1.5. [redacted]

[redacted]

[redacted]

9.5.2.2. [redacted]

9.5.2.2.1. [redacted]

[redacted]

9.5.2.2.2. [redacted]

[redacted]

9.5.3. [redacted]

[redacted]

Table 4: [redacted]

[redacted]

9.5.3.1. [redacted]

[redacted]

9.5.4. [redacted]

[redacted]

9.5.4.1. [redacted]

[redacted]

9.5.4.1.1. [redacted]

[redacted]

10. ADVERSE EVENTS

All AEs, whether observed by the investigator, reported by the subject, noted from laboratory findings, or identified by other means, will be recorded from the time the subject has signed the ICF until the subject's final study visit (or upon early termination).

10.1. Definition

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign

(including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

AEs include, but are not limited to, any of the following:

- worsening or change in nature, severity, or frequency of conditions present at the start of the study
- subject deterioration beyond what would be expected due to the primary illness
- intercurrent illness
- drug interaction

All suicidal behaviors and clinically significant suicidal ideations will be documented as an AE.

Subjects should be questioned in a general way, without asking about the occurrence of any specific symptom. The investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE and not the individual signs/symptoms. Following questioning and evaluation, all AEs, whether believed by the investigator to be related or unrelated to the study treatment, must be documented in the subject's medical records, in accordance with the investigator's normal clinical practice and on the AE eCRF. Each AE is to be evaluated for duration, intensity, frequency, seriousness, outcome, other actions taken, and relationship to the study treatment.

The following are not considered AEs:

- Continuous persistent disease/symptom present before drug administration, unless it unexpectedly progresses, or increases in severity following drug administration.
- Treatment failure or lack of efficacy
- Seizures will not be considered an AE unless there is a significant increase in seizure frequency, a new seizure type, occurrence of status epilepticus, and/or in the investigator's opinion it should be captured as an AE.
- Pregnancy
- Overdose of either study treatment or concomitant medication without any clinical signs or symptoms.

10.1.1. Intensity of Adverse Events

AEs must be graded for intensity. An intensity category of mild, moderate, or severe, as defined in Table 5, must be entered on the AE eCRF. It should be noted that the term "severe" used to grade intensity is not synonymous with the term "serious."

Table 5: Intensity of Adverse Events

Grade	Intensity
Mild	An adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	An adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.
Severe	An adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

10.1.2. Relationship to Study Treatment

The investigator will document his/her opinion of the relationship of the AE to study treatment using the criteria outlined in Table 6. An AE is deemed associated with the use of the study treatment "if there is a reasonable possibility that the drug caused the AE" (otherwise referred to as a suspected adverse reaction). Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the AE (Title 21 Code of Federal Regulations [CFR] 312.32 [a]).

Table 6: Relationship of Adverse Events to Study Treatment

Relationship	Description
Definite	The adverse event (AE) follows a reasonable temporal sequence from administration of the drug, abates upon discontinuation of the drug, follows a known or hypothesized cause-effect relationship, and (if appropriate) reappears when the drug is reintroduced.
Possible	The AE follows a reasonable temporal sequence from administration of the drug and cannot be reasonably explained by the known characteristics of the subject's clinical state, environmental, or toxic factors, or other modes of therapy administered to the subject. There should be some evidence to support a causal relationship between the drug and the adverse event.
Unlikely	The temporal sequence between the AE and the drug is such that the drug is not likely to have any reasonable association with the AE or other plausible explanations exist for the AE (eg, disease, other drugs).
Not Related	The AE does not follow a reasonable temporal sequence from administration of the drug, may not abate upon discontinuation of the drug, does not follow a known or hypothesized cause-effect relationship, and (if applicable) may not reappear when the drug is reintroduced, furthermore, there may exist a clear alternative medical explanation (eg, underlying disease state) or association with study procedure or study conduct.

10.2. Recording Adverse Events

For randomized subjects, each AE will be listed as a separate entry on an AE eCRF. Screen failure subjects will have AE information noted only in the source document. The investigator (or designee) will provide information on dates of onset and resolution, intensity, seriousness, frequency, action(s) taken, changes in study treatment usage, relationship to study treatment, and outcome.

The following categories of medical events that could occur during participation in a clinical study must be reported within 24 hours to NBI or its designee:

- SAE, including death (must be reported immediately and no later than 24 hours under any circumstances)
- Pregnancy
- Treatment unblinding for any reason.
- Events of suicidal behavior or suicidal ideation type 4 (active suicidal ideation with some intent to act, without specific plan) or type 5 (active suicidal ideation with specific plan and intent) based on the C-SSRS.

10.3. Poststudy Follow-Up of Adverse Events

All AEs, including clinically significant changes in ECGs, physical examination findings, or isolated clinically significant laboratory findings must be followed until the event resolves, the condition stabilizes, the event is otherwise explained, or the subject is lost to follow-up.

AEs ongoing at the final visit or at early termination will be followed for as long as necessary to adequately evaluate the subject's safety or until the event stabilizes, resolves, or the subject is lost to follow-up. The investigator is responsible for ensuring that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals, as is practical.

10.4. Serious Adverse Events

All SAEs will be recorded from the time the subject has signed the ICF until the final study visit. Investigators are not obligated to actively seek SAEs after a subject has withdrawn from or completed the study. However, if the investigator learns of any SAE, including a death, at any time after a subject has been withdrawn from or has completed the study, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor as described in Section 10.4.3.

10.4.1. Definition of a Serious Adverse Event

An SAE is any AE that results in any of the following outcome:

- Death.
- A life-threatening AE. Life-threatening means that the subject was, in the view of the investigator or Sponsor, at immediate risk of death from the reaction as it occurred. It does not mean that hypothetically the event might have caused death if it occurred in a more serious form.
- Inpatient hospitalization or prolongation of existing hospitalization. Hospitalization for elective treatment or a pre-existing condition that did not worsen during the clinical investigation is not considered an AE. Hospitalization or nursing home admission for the purpose of caregiver respite is not considered an AE. Complications

that occur during hospitalization are AEs, and if a complication prolongs hospitalization, the event is considered serious. Treatment in a hospital emergency room is not a hospitalization.

- A persistent or significant incapacity or substantial disruption of a person's ability to conduct normal life functions.
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization. These events may be considered serious when, based on appropriate medical judgment, they may jeopardize the health of the subject and may require medical or surgical intervention to prevent one of the outcomes listed. Any other event thought by the investigator to be serious should also be reported, following the reporting requirements detailed in this section. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

10.4.2. Managing Serious Adverse Events

Subjects experiencing an SAE or an emergency situation will be examined by a physician as soon as possible. The physician in attendance will do whatever is medically needed for the safety and well-being of the subject. The subject will remain under observation as long as medically indicated. Appropriate laboratory studies will be conducted until all parameters return to normal or are otherwise explained or stable. The subject will be followed until the SAE resolves or until the subject is medically stabilized. The investigator (or designee) will notify the Study Medical Monitor of the SAE and the outcome of the SAE immediately and no later than 24 hours under any circumstances and will also notify the IRB/IEC, if necessary.

10.4.3. Reporting Serious Adverse Events and Other Immediately Reportable Events

SAEs must be reported immediately and no later than 24 hours under any circumstances, and other immediately reportable events (defined in Section 10.4) must be reported within 24 hours of first knowledge of the event by study personnel to the Study Medical Monitor and NBI Drug Safety and Pharmacovigilance (DSPV) Department. Reports of SAEs and pregnancies must be followed by a fax or email of the SAE or Pregnancy Form. It is important that the investigator provides his or her assessment of relationship to study treatment at the time of the initial SAE report.

For SAEs and pregnancies, contact DSPV (Table 7). Treatment unblinding and events of suicidal behavior or suicidal ideation type 4 or 5 based on the C-SSRS should be reported to the Study Medical Monitor (Table 7).

Table 7: Contact Information for Drug Safety and Pharmacovigilance and Study Medical Monitor

DSPV Facsimile Email	[redacted]
Study Medical Monitor	[redacted] Telephone: [redacted] US toll free: [redacted] Email: [redacted]

10.4.4. Expedited Safety Reports

NBI or its representatives will submit an Expedited Safety Report for any suspected adverse reaction (as defined in Section 10.1.2) that is considered both serious and unexpected within 15 calendar days and for any unexpected fatal or life-threatening experience within 7 calendar days to the applicable regulatory authority(ies); or according to country-specific regulations.

NBI or its representatives will send copies of each safety report submitted to regulatory authorities to the investigators. The safety report must be submitted to the appropriate IRB/IEC as soon as possible. Documentation of the submission to the IRB/IEC and receipt by the IRB/IEC (if applicable) must be retained for each safety report.

10.5. Pregnancy

Pregnancy is neither an AE nor an SAE unless the criteria for an SAE are met. However, all pregnancies in subjects who received NBI-921352 will be followed to assess for congenital anomaly. Subjects of child bearing potential must be counseled at all visits to continue using contraception (inclusion criterion #13, Section 5.1) until 30 days after the last dose of study treatment. If a subject believes she is pregnant at any time between the time the subject signs the ICF and the last study visit, she should return to the study center within 24 hours and undergo a serum pregnancy test. Subjects confirmed to be pregnant will be unblinded.

All confirmed pregnancies in subjects who received study treatment must be immediately reported to NBI (Section 10.4.3 for contact information), followed by fax or email of the pregnancy form to NBI DSPV. A first trimester ultrasound will be requested for all confirmed pregnancies. Pregnancies in subjects who received NBI-921352 will be followed until resolution (ie, termination [voluntary or spontaneous] or birth).

11. STATISTICAL METHODS

This section is a summary of the planned statistical analyses of the endpoints. The statistical analysis plan (SAP) will be finalized prior to database lock and will include a more technical and detailed description of the analyses described in this section.

11.1. Sample Size Determination

The sample size estimates are based on the total number of subjects that will be included in the primary analysis.

11.2. Analysis Sets

The analysis sets to be used for the analyses described in this protocol are defined in Table 8. Additional analysis sets may be specified in the SAP.

Table 8: Analysis Sets

Subject Analysis Set	Description
Full Analysis Set	The FAS will include all subjects who are randomized, receive study treatment, and have post-baseline efficacy data. Subjects will be analyzed according to their randomized treatment group. Subjects in the Sentinel Cohort may be excluded from the primary analysis of efficacy data if changes to dosing are implemented in the Main Cohort.
PK	The PK analysis set will include all subjects who are administered NBI-921352, have at least 1 reportable plasma concentration value for NBI-921352, and do not have any important protocol deviations that exclude them from the PK analysis.
Safety	The safety analysis set will include all subjects who receive at least 1 dose of study treatment. Subjects will be analyzed according to their randomized treatment group, unless they receive the incorrect study treatment for the entire treatment duration.

FAS=full analysis set; PK=pharmacokinetics.

11.3. Endpoints

For the endpoints below, countable motor seizures are defined as GTCS, tonic, atonic or FOS with noticeable motor component, and noncountable seizures include absence, myoclonic, and epileptic spasms. The treatment period is defined as the [redacted] titration period and the [redacted] maintenance period combined.

11.3.1. Primary

- Percentage change from baseline in 28-day seizure frequency for countable motor seizures during the treatment period of the study.

11.3.2. Key Secondary

- Treatment response defined as a ≥50% decrease from baseline in 28-day seizure frequency for countable motor seizures during the treatment period of the study.

11.3.3. Other Secondary

- Percentage change from baseline in 28-day seizure frequency for countable motor seizures, during the [redacted] of the maintenance period.
- Treatment response defined as a ≥25%, ≥75%, or 100% decrease from baseline in 28-day seizure frequency for countable motor seizures during the treatment period of the study.
- Treatment response defined as a ≥25%, ≥50%, ≥75%, or 100% decrease from baseline in 28-day seizure frequency for countable motor seizures during the maintenance period of the study.
- CGIC and Parent/Caregiver GIC at each study visit during the treatment period of the study.
- Change from baseline in CGIS and Parent/Caregiver GIS at each visit during the treatment period of the study.

11.3.4. Exploratory

[redacted]

[redacted]

11.3.5. Pharmacokinetics

- PK parameters for NBI-921352 and metabolites will be determined by standard noncompartmental methods.
- Plasma concentration data for NBI-921352 [redacted]
- [redacted]

11.3.6. Safety

- Incidence of adverse events and suicidality (as measured by either C-SSRS or clinical report of AEs of suicidality depending on subject's age and developmental level).
- Absolute values and changes from baseline in clinical laboratory test values (hematology and clinical chemistry), vital signs, weight, Tanner stage, and ECG parameters.
- [redacted]

11.4. Statistical Analyses

Descriptive and inferential statistical methods will be used to evaluate and summarize the data from this study. Descriptive statistics typically refers to the number of subjects (n), mean, standard deviation (SD) or standard error (SE), median, first (Q1) and third (Q3) quartile, minimum, maximum, and confidence intervals for continuous variables; and refers to the number and percentage of subjects for categorical variables. Inferential statistics refers to the analysis results from hypothesis tests, which will be performed to assess differences between treatment groups (NBI-921352 and placebo).

Statistical analyses for the study endpoints are summarized in Table 9.

Table 9: Endpoints and Statistical Methods

Endpoint	Statistical Methodology
Primary	The primary endpoint is the percentage change from baseline in 28-day seizure frequency for countable motor seizures during the treatment period. Percentage change from baseline will be calculated as ((Frequency during the treatment period – Frequency during baseline) ÷ Frequency during baseline) × 100, where frequency during each period is calculated as (Number of seizures in the period ÷ Number of nonmissing days in the period) × 28.

Endpoint	Statistical Methodology
	The null hypothesis is the percentage reduction from baseline in 28-day seizure frequency during the treatment period in subjects treated with NBI-921352 is equal to the reduction in subjects treated with placebo. The null hypothesis of no treatment effect will be tested using a Wilcoxon rank-sum test (2-sided test) at the [redacted] significance level. An estimate of the median difference between NBI-921352 and placebo, [redacted], will be presented.
Key Secondary	The proportion of subjects considered treatment responders, defined as a ≥50% decrease from baseline in 28-day seizure frequency for countable motor seizures during the treatment period, will be summarized by treatment group and analyzed using Fisher's exact test. In addition, the difference in proportions and the odds ratio (NBI-921352 vs. placebo) will be presented with 95% confidence intervals.
Secondary	Secondary endpoints will be compared between treatment groups over the 16-week treatment period using appropriate statistical methodology as described in the SAP.
Safety	A TEAE is an adverse event that started or worsened in severity following the first dose of study treatment. Subject incidence of TEAEs, serious TEAEs, TEAEs leading to discontinuation of study treatment, fatal TEAEs, and adverse events of special interest will be summarized for each treatment group by system organ class and preferred term. Clinical laboratory, vital signs, ECG, weight, height/length, Tanner stage, C-SSRS, [redacted] at baseline and during treatment, and the changes from baseline, will be summarized for each treatment group using descriptive statistics. The incidence of potentially clinically significant laboratory values will be provided. Categorical shift tables for selected laboratory values may also be presented.
PK	The plasma concentration data for NBI-921352 and metabolites will be summarized by sampling time point using the PK Analysis Set. [redacted]

ASM=antiseizure medication; BLQ=below the level of quantification; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; PK=pharmacokinetics; SAP=statistical analysis plan; TEAE=treatment-emergent adverse event; VABS-3=Vineland Adaptive Behavioral Scales-3.

11.4.1. Missing Data

The primary and key secondary endpoints are calculated from the available data collected during the treatment period. Any sensitivity analyses to explore the robustness of the primary analysis will be specified in the SAP. Any methods of handling missing data in the secondary and exploratory endpoints will be specified in the SAP.

11.4.2. Interim Analysis

A review of the unblinded Sentinel Cohort data (including safety, tolerability, and PK data [PK data will only be assessed at [redacted] will be conducted by the independent DMC. The DMC will also conduct an ongoing review of safety and tolerability data for both the Sentinel and Main Cohorts. The DMC has the overall responsibility of safeguarding the interests of the subjects by monitoring data obtained in the study and making appropriate recommendations based on the reported data, thus ensuring that the study is being conducted with high scientific and ethical standards. Provisions will be in place to maintain the blinding of Sponsor study personnel. The DMC charter will describe the responsibilities, timing of meetings, and data review procedures for the members to follow.

The first 8 subjects (randomized 1:1; ie, 4 subjects randomized to NBI-921352 and 4 subjects randomized to placebo) will be enrolled into the Sentinel Cohort for the analysis of safety, tolerability, and PK data through [redacted] by the DMC. Efficacy analyses will not be performed as part of this analysis.

12. SUPPORTING DOCUMENTATION

12.1. Case Report Forms

The eCRF data for this study are being collected with an electronic data capture (EDC) system (Rave®) provided by Medidata Solutions Incorporated, NY, USA. The EDC system and the study-specific eCRFs will comply with FDA Title 21 CFR Part 11 and Articles 25, 26, 28, and 32 of the EU GDPR. The documentation related to the validation of the EDC system is available through the vendor, Medidata, while the validation of the study specific eCRFs will be conducted by NBI and the required documentation will be maintained in the Trial Master File.

The investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All eCRF data required by this protocol will be recorded by authorized study personnel in the EDC system, with the exception of data captured in an electronic format, which will be loaded electronically into the appropriate eCRFs. All data entered into the eCRF will be supported by source documentation. The investigator should review the eCRFs as soon as possible after the subject visit has occurred and should electronically sign the eCRFs as soon as possible after the subject completes or withdraws from the study.

The investigator or an authorized member of the investigator's staff will make any necessary additions/corrections to the eCRF. All change information, including the date, person performing the corrections, and reason for the change will be available via the electronic audit trail, which is part of the EDC system. The eCRFs will be reviewed periodically for completeness, legibility, and acceptability by NBI (or designee). NBI will also be allowed access to all source documents and medical records pertinent to the study in order to verify eCRF entries. The Principal Investigator will review the eCRFs for completeness and accuracy and enter his or her electronic signature on the eCRFs as evidence thereof.

Medidata will provide access to the NBI portal of the EDC system for the duration of the study through a password-protected method of internet access. Such access will be removed from study centers at the end of the center's participation in the study. Data from the EDC system will be archived on appropriate data media or uploaded to a secure location with restricted access, in order to provide the investigator with a durable record of the center's eCRF data. Although not required, the investigator may make paper printouts from that media.

All clinical work conducted under this protocol is subject to GCP regulations. This includes an inspection by NBI and/or health authority representatives at any time. The Principal Investigator will agree to the inspection of study-related records by health authority representatives and/or NBI.

12.2. Data Capture, Review, and Validation

Data entered in the EDC system will be verified against the source data by NBI (or designee). Any discrepancies will be corrected on-line by authorized study center personnel. After data is entered into the EDC, automated (computer-generated) logic checks will run in order to identify items such as inconsistent study dates. In addition, manual review/checks may be performed by NBI on the data. Any inconsistencies/errors/omissions identified will be sent to the study center (via an electronic query) for the necessary corrections to be made to the eCRF. Once entered and saved in an eCRF, data immediately become part of the study database and are available to NBI.

12.3. Coding Dictionaries

AEs and medical history will be coded using the chosen version of the Medical Dictionary for Regulatory Activities (MedDRA), per NBI. Prior and concomitant medications will be coded using the chosen version of the World Health Organization Drug Dictionary, per NBI.

12.4. Ethics

The Sponsor personnel and the investigators will ensure that the study is conducted in full compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines, and with the laws and regulations of the country in which the study is conducted.

The investigator and/or Sponsor/CRO will submit this protocol and any related document(s) to be provided to the subject to an IEC/IRB and to the national competent (health) authority (as applicable). Approval documentation (as applicable) from both the IEC/IRB and the national competent (health) authority must be obtained before starting the study.

12.5. General Legal References

The study will be carried out according to provisions of the United States (US) CFR, the US Food and Drug Administration (FDA), the laws and regulations of the country in which the study is conducted, and the ICH Guidelines for GCP. All clinical work conducted under this protocol is subject to GCP regulations. This includes an inspection by the Sponsor or its representative, health authority, or IRB/IEC representatives at any time. The investigator must agree to the inspection of study related records by health authority representatives and/or the Sponsor or its designee.

12.6. Institutional Review Board/Independent Ethics Committee

The final approved protocol and the ICF will be reviewed by the IRB/IEC at the study center. The committee's decision concerning conduct of the study will be sent in writing to the investigator and a copy will be forwarded to the Sponsor. The investigator must agree to make any required progress reports to the IRB/IEC, as well as reports of SAEs, life-threatening problems, or death.

A list of members participating in the IEC/IRB meetings must be provided, including the names, qualifications, and functions of these members. If that is not possible, the attempts made to obtain this information along with an explanation as to why it cannot be obtained or disclosed must be documented in the study documentation.

If a member of the site study personnel was present during an IEC/IRB meeting, it must be clear that this person did not vote.

12.7. Protocol Adherence – Amendments

The protocol must be read thoroughly, and the instructions must be followed exactly. Any changes in the protocol will require a formal amendment. Such amendments will be agreed upon and approved in writing by the investigator and the Sponsor. The IRB/IEC and local health authorities will be notified of all amendments to the protocol in accordance with local regulations.

Modifications made to the protocol or the ICF after receipt of the approval must also be submitted as amendments by the investigator and/or Sponsor/CRO to the IEC/IRB and to the national competent (health) authority and approved prior to implementation, as applicable, in accordance with local procedures and regulations.

12.8. Required Documents

The investigator must provide NBI or its designee with the following documents before the enrollment of any subject (originals should be kept by the investigator in the investigator's study regulatory document binder):

- Signed copy of the protocol signature page.
- Investigator's Brochure acknowledgement page.
- Completed and signed statement of investigator qualifications, as applicable.

- Financial disclosure documentation as required.
- Curriculum vitae and current medical license of the investigator and subinvestigators.
- Letter of approval from the IRB/IEC for protocol and consent form.
- Copy of the IRB/IEC approved written ICF to be used.
- Laboratory documents (certifications/accreditations, normal ranges) if not provided by a central laboratory.

12.9. Informed Consent/Assent

The subject's parent(s) or legal guardian(s) will provide informed consent with signed and witnessed pediatric assent for subjects <18 years of age determined by the investigator to be capable of providing assent and for subjects ≥18 years of age who are not capable of providing consent according to national laws and regulations before the performance of any study related procedures. Subjects who are ≥18 years of age and capable of providing consent will provide informed consent. Informed consent/assent may be done remotely by the investigator or designee, only if allowed by national laws and regulations and institutional guidelines and remote consenting procedures are in place.

Each subject's chart will include the signed ICF for study participation. When the study treatment is completed and the eCRF has been monitored, the ICF will be kept in the investigator's central study file. Regulatory authorities may check the existence of the signed ICF in this central study folder if not having done so during the study.

12.10. Study Monitoring

Throughout the course of the study, the study monitor will make frequent contacts with the investigator. This will include telephone calls and on-site visits. During the on-site visits, the eCRFs will be reviewed for completeness and adherence to the protocol. As part of the data audit, source documents will be made available for review by the study monitor. The study monitor will also perform drug accountability checks and may periodically request review of the investigator study file to ensure completeness of documentation in all respects of clinical study conduct.

Upon completion of the study, the study monitor will arrange for a final review of the study files after which the files should be secured for the appropriate time period. The investigator or appointed delegate will receive the study monitor during these on-site visits, will cooperate in providing the documents for inspection, and will respond to inquiries. In addition, the investigator will permit inspection of the study files by authorized representatives of the regulatory agencies.

12.11. Quality Assurance

The study will be conducted in accordance with NBI's standard operating procedures designed to ensure that all procedures are in compliance with GCP and FDA Guidelines, and the laws and regulations of the country in which the study is conducted. Quality assurance audits may be performed at the discretion of NBI.

12.12. Record Retention

Study records should be retained in compliance with the federal regulations of the clinical site.

NBI may request these records to be retained for a longer period if required by applicable regulatory requirements or Sponsor contractual obligations. If the investigator is unable to retain the study documents for the required amount of time, NBI must be informed of the individual who will be assuming this responsibility.

12.13. Confidentiality

NBI or its designee, and the study center affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, all data will be identified only by an identification number.

All information concerning this study and which was not previously published is considered confidential information. This confidential information shall remain the sole property of NBI; it shall not be disclosed to others without written consent of NBI; and shall not be used except in the performance of this study.

The information compiled during the conduct of this clinical study is also considered confidential and may be disclosed and/or used only by NBI as deemed necessary. To allow the use of the information derived from this clinical study and to ensure compliance the laws and regulations of the country in which the study is conducted, the investigator is obliged to furnish NBI with the complete test results and all data compiled in this study.

12.14. Publication Policy

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

13. STUDY COMMENCEMENT AND DISCONTINUATION

Upon satisfactory receipt of all required regulatory documents, NBI (or designee) will arrange that all study materials be delivered to the study site. Subject entry should not begin until after the required regulatory documents are confirmed as received and the Investigator Meeting/Initiation Meeting has occurred. All personnel expected to be involved in the conduct of the study will undergo orientation to include review of the study protocol, instructions for eCRF completion, AE reporting, and overall responsibilities including those for drug accountability and study file maintenance.

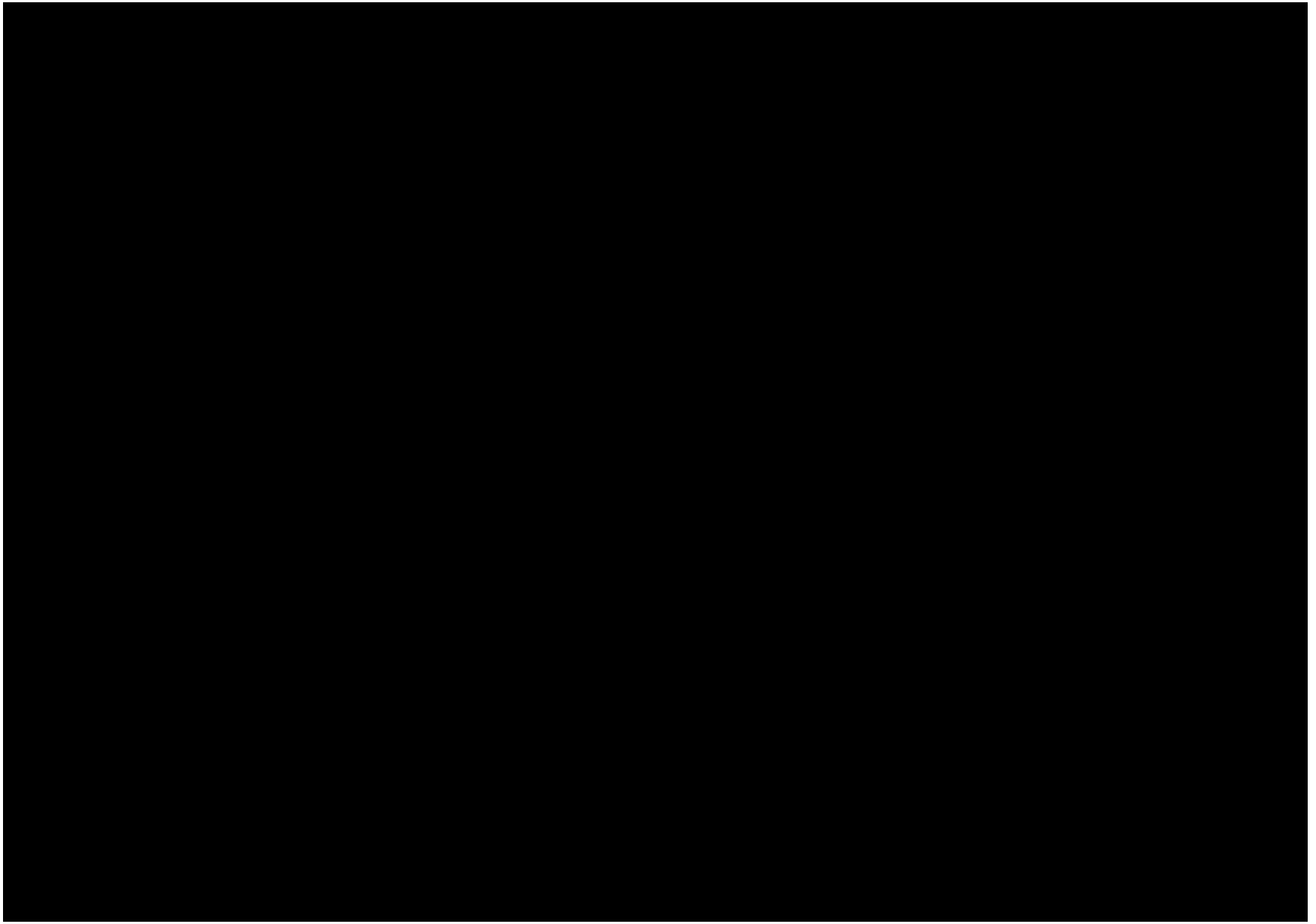
If the study is discontinued, all subjects should undergo a complete follow-up examination. Any clinically relevant finding, including laboratory values of potential clinical concern, and adverse experiences will be followed until they resolve or return to a clinically acceptable level.

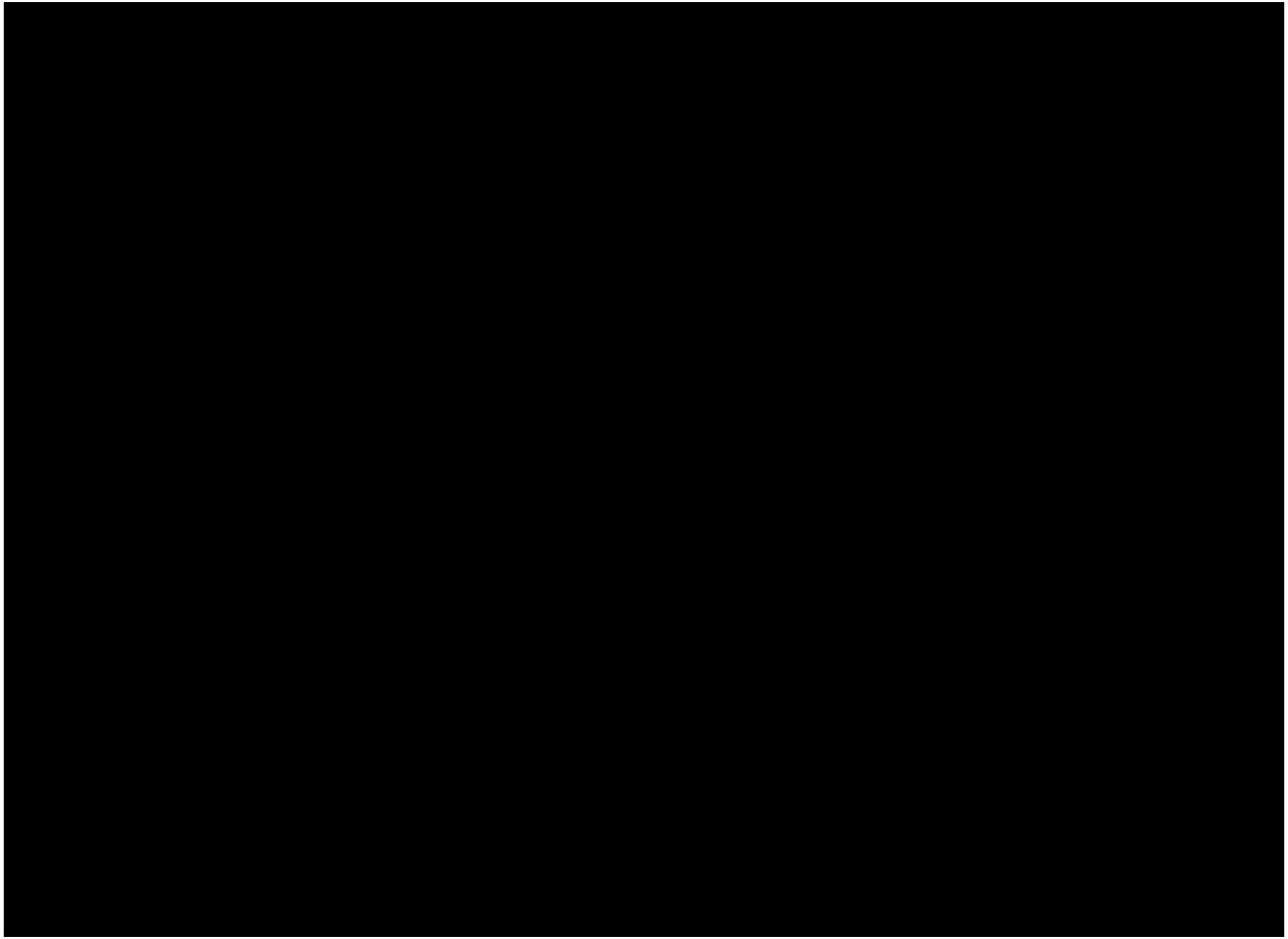
14. [redacted]

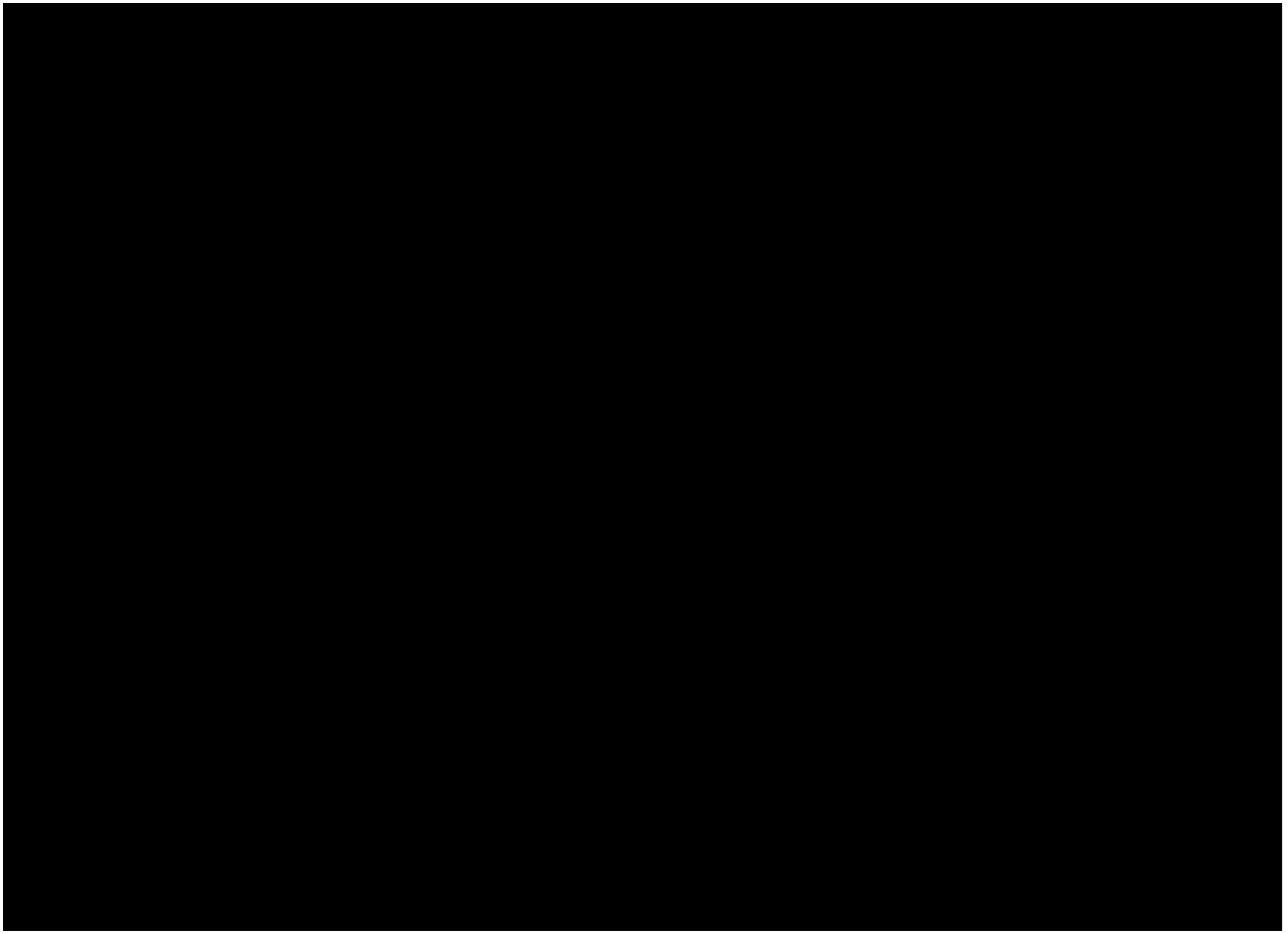
APPENDIX A. SCHEDULE OF ASSESSMENTS

Table 10: [redacted]

[redacted]







APPENDIX B. INVESTIGATORS SIGNATURE

CLINICAL STUDY TITLE: A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, Tolerability, and Pharmacokinetics of NBI-921352 as Adjunctive Therapy in Subjects with SCN8A Developmental and Epileptic Encephalopathy Syndrome (SCN8A-DEE)

PROTOCOL No.: NBI-921352-DEE2012

As Agreed:

_____ _____

Principal Investigator Signature Date

PRINCIPAL INVESTIGATOR:

_____

(Print Principal Investigator Name)

STUDY CENTER:

_____

(Print Study Center Name)

APPENDIX C. SPONSORS APPROVAL SIGNATURE

Accepted for the Sponsor:

SPONSOR: Neurocrine Biosciences, Inc.

[redacted]

Telephone: [redacted]
Facsimile: [redacted]

[redacted]

Neurocrine Biosciences, Inc.

[redacted]