CLINICAL STUDY PROTOCOL

Phase 2 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Efficacy, Safety, Tolerability, and Pharmacokinetics of NBI-827104 in Pediatric Subjects with Epileptic Encephalopathy with Continuous Spike-and-Wave During Sleep

Study No.: NBI-827104-CSWS2010

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EudraCT# 2020-003141-11

Amendment 3.0 (05 August 2021)

Amendment 2.0 (03 May 2021)

Amendment 1 (19 June 2020)

Original Protocol (30 September 2019)

Development Phase: 2

Study Sponsor: Neurocrine Biosciences, Inc.
[redacted]
Telephone: [redacted]
Facsimile: [redacted]

SIGNATURES:

I agree to conduct this study in accordance with the requirements of this Clinical Study Protocol and in accordance with the following:

- Established principles of International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practices (GCP)
- All applicable laws and regulations

CLINICAL STUDY TITLE: Phase 2 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Efficacy, Safety, Tolerability, and Pharmacokinetics of NBI-827104 in Pediatric Subjects with Epileptic Encephalopathy with Continuous Spike-and-Wave During Sleep

PROTOCOL No.: NBI-827104-CSWS2010

As Agreed:

_____ _____

Principal Investigator Signature Date

PRINCIPAL INVESTIGATOR:

_____

(Print Principal Investigator Name)

CENTER:

_____

(Print Study Center Name)

Accepted for the Study Sponsor:

STUDY SPONSOR: Neurocrine Biosciences, Inc.

[redacted]

Telephone: [redacted]
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LIST OF PERSONNEL

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Facsimile:
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2. SYNOPSIS

Title of study: Phase 2 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Efficacy, Safety, Tolerability, and Pharmacokinetics of NBI-827104 in Pediatric Subjects with Epileptic Encephalopathy with Continuous Spike-and-Wave During Sleep

Protocol number: NBI-827104-CSWS2010

Phase of development: 2

Study center(s): Approximately 24 study centers in regions including, but not limited to, the United States, Europe, and Canada

Primary Objective:

- To assess the effect of NBI-827104 on the overnight epileptiform video-electroencephalogram (video-EEG) activity in pediatric subjects with epileptic encephalopathy with continuous spike-and-wave during sleep (EECSWS)

Secondary Objective:

- To evaluate the safety and tolerability of multiple doses of NBI-827104 in pediatric subjects with EECSWS

Other Objectives:

- [redacted]

Methodology: This is a Phase 2, multicenter, double-blind, placebo-controlled, parallel-group study designed to assess the efficacy, safety, tolerability, and PK of NBI-827104 in pediatric subjects with EECSWS. Approximately 24 male and female subjects, 4 to 12 years of age (inclusive), will be enrolled for study participation. Treatment will be administered for up to [redacted] including titration and taper periods.

After providing parental or legal guardian informed consent with pediatric assent from developmentally capable pediatric subjects, subjects will be screened to determine eligibility (Days -28 to -1) before the start of study treatment dosing on Day 1. Caregiver(s) will be given a seizure diary at screening, Day 1, and [redacted] and caregiver(s) will return the seizure diary at the next scheduled visit. At least 4 days of baseline seizure diary data should be obtained prior to randomization. On Day 1, eligible subjects who have a diagnosis confirmed by an external Diagnosis Confirmation Panel (DCP) will return to the study center for collection of baseline safety and efficacy assessments. Subjects who are confirmed as eligible will then be randomized to NBI-827104 or placebo. The first 6 subjects (randomized 2:1; ie, 4 subjects randomized to NBI-827104 and 2 subjects randomized to placebo) will be enrolled into a sentinel cohort for the analysis of safety, tolerability, and PK data through the end of [redacted] followed by the remaining 18 subjects in the main cohort (randomized 2:1 [NBI-827104:placebo]). Study treatment will last for up to [redacted]

- [redacted]

If an open-label extension (OLE) study is open for enrollment, eligible subjects may enter the OLE study following the completion of the [redacted] study visit at the end of the maintenance period. For subjects who enroll directly in the OLE study, the [redacted] visit will be the final study visit of the current study. For all other subjects, the end of the posttreatment safety period constitutes the end of the study.

The starting dose of study treatment for the sentinel cohort (dose level 1) will be based on body weight categories (based on subjects' body weight on Day 1), as detailed in the table below. [redacted] Based on the exposure data obtained from the sentinel cohort, the doses may be adjusted if required to achieve the targeted exposure in the main cohort.

[redacted]

[redacted] Subjects who cannot tolerate the lowest allowable dose (ie, dose level 1) should remain in the study, but study treatment dosing will be discontinued.

At the [redacted] visit, subjects will receive study treatment to administer at home during the taper period. [redacted]

During the posttreatment safety period, subjects/caregivers will be instructed to:

- Contact the investigator (or designee) if symptoms worsen and require medical attention
- Report any adverse events (AEs) or serious adverse events (SAEs)

[redacted]

Safety and tolerability assessments including AE monitoring, clinical laboratory tests (including hematology, serum chemistry, and urinalysis), vital signs measurements, physical and neurological examinations, 12-lead electrocardiograms (ECGs), and ophthalmic examinations will be conducted throughout the study.

Ongoing review of safety and tolerability data and the unblinded analysis of sentinel cohort data (including safety and tolerability) will be conducted by the Independent Data Monitoring Committee (IDMC); sentinel cohort data (including PK data) will be evaluated before proceeding to the main cohort. The IDMC 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. Study site personnel and the Sponsor (except for supply chain personnel not involved in decisions regarding subject treatment) will remain blinded.

Available PK and safety data for the sentinel cohort will be reviewed by the IDMC to determine if a dose adjustment should be instituted prior to enrolling the main cohort. Dose reductions or alterations in the escalation paradigm may be recommended by the IDMC to the Sponsor after the sentinel cohort if the drug is not sufficiently tolerated. In addition, dose reductions or escalations may be instituted if the median exposure values for the sentinel cohort lie outside the 5th to 95th percentiles of the simulated reference range across the PK sampling intervals.

[redacted]

[redacted]

Study population: A total of approximately 24 male and female pediatric subjects, 4 to 12 years of age, inclusive, with EECSWS will be enrolled. Diagnosis of EECSWS must be confirmed by the DCP. It is estimated that 24 subjects should be randomized in order to have 21 evaluable subjects at the end of [redacted] and 18 evaluable subjects at the end of [redacted]

Duration of treatment and study participation: The expected duration of study participation for subjects who do not enroll directly into an OLE study is up to [redacted], including up to [redacted] of screening, up to [redacted] of study treatment, and a posttreatment safety period of [redacted]. The expected duration of study participation for subjects who enroll directly into an OLE study is up to [redacted], including up to [redacted] of screening and up to [redacted] of study treatment.

Investigational product, dosage and mode of administration: NBI-827104 will be provided as minitablets of [redacted]

Reference therapy, dose and mode of administration, batch number: Matching NBI-827104 placebo minitablets will be provided.

Criteria for evaluation:

Efficacy:

- Overnight video-EEG
  - SWI
  - [redacted]
  - [redacted]
- Clinical Global Impression of Change
- Caregiver Global Impression of Change
- Clinical Global Impression of Severity
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- [redacted]
- [redacted]
- [redacted]
  - [redacted]

- [redacted]

Safety:

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

- AEs
- Clinical laboratory tests (hematology, serum chemistry, and urinalysis)
- Vital signs (including blood pressure, pulse rate, and body temperature)
- Physical examinations, including neurological examinations
- 12-lead ECG
- Columbia-Suicide Severity Rating Scale, Children's Version
- Ophthalmic examinations

Statistical methods: [redacted]

Safety data will be summarized using descriptive statistics.

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
ASM	antiseizure medication
ANCOVA	analysis of covariance
ALT	alanine aminotransferase
AST	aspartate aminotransferase
[redacted]	[redacted]
β-hCG	beta-human chorionic gonadotropin
[redacted]	
CFR	Code of Federal Regulations
CGI-C	Clinical Global Impression of Change
CGI-S	Clinical Global Impression of Severity
CI	confidence interval
[redacted]	[redacted]
COVID-19	Coronavirus Disease 2019
[redacted]	[redacted]
C-SSRS	Columbia-Suicide Severity Rating Scale
CSWS	continuous spike-and-wave during sleep
[redacted]	
CV	coefficient of variation
DBP	diastolic blood pressure
DCP	Diagnosis Confirmation Panel
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSPV	Drug Safety and Pharmacovigilance
ECG	electrocardiogram

eCRF	electronic case report form
EDC	electronic data capture
EECSWS	epileptic encephalopathy with continuous spike-and-wave during sleep
EEG	electroencephalogram
EOS	end of study
[redacted]	[redacted]
ESES	electrical status epilepticus during sleep
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEC	Global Executive Composite
GGT	gamma-glutamyl transferase
GI-C	Global Impression of Change
GMR	geometric mean ratio
HBsAg	hepatitis B surface antigen
HCV-Ab	hepatitis C antibody
HIV-Ab	human immunodeficiency virus antibody or antigen
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IGE	idiopathic generalized epilepsy
IRB	Institutional Review Board
IVIG	intravenous immunoglobulin
max.	maximum
min.	minimum
MMRM	mixed model for repeated measurements
NOAEL	no observed adverse effect level
NREM	nonrapid eye movement
OLE	open-label extension
PK	pharmacokinetics
QTcF	corrected QT interval using Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan

SBP	systolic blood pressure
SD	standard deviation
[redacted]	[redacted]
SWI	spike-wave index
τ	dosing interval
T3	triiodothyronine
T4	thyroxine
[redacted]	[redacted]
[redacted]	[redacted]
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States
[redacted]	[redacted]
VNS	Vagal nerve stimulator
[redacted]	[redacted]

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/Contract Research Organization (CRO) will submit this protocol and any related document(s) provided to the parent(s) / legally designated representative and the subject to an Independent Ethics Committee (IEC) / Institutional Review Board (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.

5. INTRODUCTION

5.1. Background

Calcium is an important signal transduction element in neurons and its entry into the cell is tightly regulated by two major classes of voltage-gated calcium channels: the high-voltage activated (L-, N-, P/Q- and R-types) and the low-voltage activated (T-type) calcium channels (Catterall et al., 2005).

Three T-type calcium channel subtypes with different electrophysiological properties have been described: Cav3.1, Cav3.2 and Cav3.3 (Lee et al., 1999; Perez-Reyes, 2003) and are widely expressed in the brain (Talley et al., 1999). Under physiological conditions, T-type calcium channels promote cellular rebound bursting by de-inactivating during hyperpolarization and opening at low-voltage thresholds. With their high expression levels in both cortex and thalamus (Talley et al., 1999), these channels are positioned to regulate synchronized oscillations within the thalamocortical circuit (Cheong et al., 2013; Lambert et al., 2014).

Abnormal T-type calcium-channel-mediated oscillations can be observed during idiopathic generalized epilepsy (IGE) seizures, in particular absence seizures that are characterized by spike-wave discharges, in both humans and animals (Khosravani et al., 2006; Zamponi et al., 2010; Cheong et al., 2013). The role of T-type calcium channels in generating spike-wave discharges in the cortico-thalamocortical network in absence seizures is well described. Mutations were identified in the gene expressing the Cav3.2 subtype in patients with childhood absence epilepsy and other forms of IGE (Khosravani et al., 2006; Heron et al., 2007; Zamponi et al., 2010; Eckle et al., 2014). Several of these mutations increase the intrinsic activity of the channels, whereas others increase the intracellular trafficking of the channels to the plasma membrane; most mutations enhance calcium currents. A direct consequence of this is increased excitability in neurons that exhibit enhanced bursting activity, thereby contributing to the generation of epileptiform discharges. Several rodent models confirm the importance of the Cav3.2 channel subtype. In genetic rat models of spontaneous absence-like epilepsy (genetic absence epilepsy in rats from Strasbourg [GAERS]; Wistar Albino Glaxo from Rijswijk [WAG/Rij]), a gain-of-function mutation of the Cav3.2 gene has been reported (Powell et al., 2009), as well as elevated levels of Cav3.2 mRNA, and increased T-type calcium currents (Tsakiridou et al., 1995; Talley et al., 2000; Broicher et al., 2008; Powell et al., 2009).

Several lines of evidence also link mutations in the Cav3.1 subtype with epilepsy in humans and in rodent animal models. Genetic variants have been detected in patients with juvenile myoclonic epilepsy, another form of IGE (Lory et al., 2010). Overexpression of Cav3.1 channels in mice leads to frequent bilateral cortical seizures (Ernst et al., 2009) and Cav3.1 knockout mice are protected from absence seizures (Kim et al., 2001; Song et al., 2004). No association has been made so far between Cav3.3 subtype mutations and human epilepsy.

Disruptions in the neurotransmission of the same cortico-thalamocortical circuitry involved in absence seizures are considered to contribute also to sleep-potentiated continuous spike-wave discharges observed in epileptic encephalopathy with continuous spike-wave discharges during sleep (EECSWS) (Sánchez Fernández et al., 2012; Singhal et al., 2014). EECSWS is a spectrum of epileptic conditions (International League Against Epilepsy, 2018) sharing the following characteristics: (1) electroclinical seizures, (2) sleep potentiation of epileptiform activity, (3) neurocognitive regression/stagnation, and (4) an age-related evolution of the condition, with onset in early childhood and spontaneous improvement before puberty (Sánchez Fernández et al., 2012; De Giorgis et al., 2017; Singhal et al., 2014). The sleep potentiation of epileptiform activity leads to an electroencephalographic pattern of electrical status epilepticus during sleep (ESES), which consists of continuous spike-waves during nonrapid eye movement (NREM) sleep. This phenomenon has been suggested to interfere with normal recuperation functions of sleep, thereby adversely affecting learning abilities, language, memory, and other cognitive domains (Bölsterli et al., 2011; Bölsterli Heinzle et al., 2014; Bölsterli et al., 2017). Although the clinical seizures and ESES disappear with age (around puberty) (Morikawa et al., 1989; Saltik et al., 2005; Kobayashi et al., 2006; Loddenkemper et al., 2011), neurocognitive regression can remain (Singhal et al., 2014; Tassinari et al., 2000; Nickels et al., 2008). The extent of the neurocognitive regression seems to correlate with the duration a child had been affected by ESES (Seegmüller et al., 2012; Maltoni et al., 2016; van den Munckhof et al., 2018).

5.2. NBI-827104

NBI-827104 is a novel selective and orally available triple T-type calcium channel blocker.

NBI-827104 effectively crosses the blood-brain barrier and shows dose-dependent efficacy in 3 rodent models of generalized epilepsy, including synergistic effects when combined with established antiseizure medications (ASMs). Considering the role of T-type calcium channels in the pathophysiology of IGE and spike-wave discharges in particular, the nonclinical data, and the unmet medical need, NBI-827104 will be developed for the treatment of EECSWS.

5.3. Study and Dose Rationale

[redacted] Based on a population pharmacokinetic (PK) model, weight-based dose regimens were developed across weight categories to determine the actual daily mg doses to be administered based on individual subject body weight.

The maximum exposure level for all subjects will be the target exposure level [redacted] The doses for the sentinel cohort (Table 1) were calculated based on a population PK model. After [redacted] PK data are assessed in the sentinel cohort, doses for the main cohort may be adjusted to achieve the target exposure level. Dose reductions or alterations in the escalation paradigm may be implemented after the sentinel cohort if the drug is not sufficiently tolerated.

5.4. Benefit-Risk Assessment

EECSWS is a spectrum of epileptic conditions (International League Against Epilepsy, 2018) with onset in early childhood and include sleep potentiation of epileptiform activity. The potentiation of epileptiform activity during sleep leads to an electroencephalogram (EEG) pattern of electrical status epilepticus during sleep (ESES), which consists of continuous spike-waves during non-REM sleep and has been suggested to interfere with normal recuperation functions of sleep, thereby adversely affecting learning abilities, language, memory, and other cognitive domains (Bölsterli et al., 2011; Bölsterli Heinzle et al., 2014; Bölsterli et al., 2017). Although spontaneous improvement before puberty is observed with EECSWS, neurocognitive regression can remain (Singhal et al., 2014; Tassinari et al., 2000; Nickels et al., 2008).

Abnormal T-type calcium channel oscillations have been implicated in the pathophysiology of IGE and spike-wave discharges, in particular. As a novel selective and orally available triple T--type calcium channel blocker which effectively crosses the blood-brain barrier, NBI-827104 may be effective in the treatment of EECSWS. NBI-827104 has demonstrated efficacy in 3 rodent models of generalized epilepsy, including synergistic effects when combined with established ASMs. The current study will be the first clinical study to evaluate efficacy of NBI-827104 in pediatric subjects with EECSWS.

[redacted]

There are no approved treatments for pediatric patients with EECSWS. Considering the role of T-type calcium channels in the pathophysiology of spike-wave discharges, the nonclinical and clinical data, and the unmet medical need, NBI-827104 is being developed for the treatment of pediatric subjects with EECSWS. This is a randomized, placebo-controlled study that includes a sentinel cohort of 6 subjects that allows the analysis of safety, tolerability, and PK data through [redacted] of the study before enrolling additional subjects. The randomization scheme of 2:1 (NBI-827104:placebo) enables a higher proportion of subjects to receive active treatment while still allowing for assessment of efficacy, safety, and tolerability in a randomized, placebo-controlled study design. The study includes appropriate safety monitoring throughout the study, including assessment of suicidal behavior and ideation using the Children's Columbia-Suicide Severity Rating Scale (C-SSRS) as appropriate and ophthalmic examinations as noted above.

6. STUDY OBJECTIVES

Primary Objective:

- To assess the effect of NBI-827104 on the overnight epileptiform video-electroencephalogram (video-EEG) activity in pediatric subjects with EECSWS

Secondary Objective:

- To evaluate the safety and tolerability of multiple doses of NBI-827104 in pediatric subjects with EECSWS

Other Objectives:

- [redacted]

- [redacted]

7. STUDY DESIGN

This is a Phase 2, multicenter, double-blind, placebo-controlled, parallel-group study designed to assess the efficacy, safety, tolerability, and PK of NBI-827104 in pediatric subjects with EECSWS. Approximately 24 male and female subjects, aged 4 to 12 years (inclusive), will be enrolled for study participation. Treatment will be administered for up to [redacted] including titration and taper periods.

After providing parental or legal guardian informed consent with pediatric assent from developmentally capable pediatric subjects, subjects will be screened to determine eligibility (Days -28 to -1) before the start of study treatment dosing on Day 1. Caregiver(s) will be given a seizure diary [redacted], and caregiver(s) will return the seizure diary at the next scheduled visit. At least 4 days of baseline seizure diary data should be obtained prior to randomization. On Day 1, eligible subjects who have a diagnosis confirmed by an external Diagnosis Confirmation Panel (DCP) will return to the study center for collection of baseline safety and efficacy assessments. Subjects who are confirmed as eligible for the study will then be randomized to NBI-827104 or placebo. The first 6 subjects (randomized 2:1; ie, 4 subjects randomized to NBI-827104 and 2 subjects randomized to placebo) will be enrolled into a sentinel cohort for the analysis of safety, tolerability, and PK data through the end of [redacted] followed by the remaining 18 subjects in the main cohort (randomized 2:1 [NBI-827104:placebo]). Study treatment will last for up to [redacted], [redacted]

- [redacted]

If an open-label extension (OLE) study is open for enrollment, eligible subjects may enter the OLE study following the completion of the [redacted] study visit at the end of the maintenance period. For subjects who enroll directly in the OLE study, the [redacted] visit will be the final study visit of the current study. For all other subjects, the end of the posttreatment safety period constitutes the end of the study.

The starting dose of study treatment for the sentinel cohort (dose level 1) will be based on body weight categories (based on subjects' body weight on Day 1), as detailed in Table 1. This study intends to target exposures equivalent to those observed [redacted] in adults [redacted] Based on the exposure

data obtained from the sentinel cohort, the doses may be adjusted if required to achieve the targeted exposure in the main cohort.

Table 1: [redacted]

[redacted]

Subjects who cannot tolerate the lowest allowable study dose (ie, dose level 1) should remain in the study but study treatment dosing will be discontinued.

At the [redacted] visit, subjects will receive study treatment to administer at home during the taper period. [redacted] During the posttreatment safety period, subjects/caregivers will be instructed to:

- Contact the investigator (or designee) if symptoms worsen and require medical attention
- Report any adverse events (AEs) or serious adverse events (SAEs)

[redacted]

Safety and tolerability assessments including AE monitoring, clinical laboratory tests (including hematology, serum chemistry, and urinalysis), vital signs measurements, physical and neurological examinations, 12-lead electrocardiogram (ECG), and ophthalmic examinations will be conducted throughout the study.

Ongoing review of unblinded safety and tolerability data and the analysis of sentinel cohort data (including safety, tolerability) will be conducted by the Independent Data Monitoring Committee

(IDMC); sentinel cohort data (including PK data) will be evaluated before proceeding to the main cohort. The IDMC 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. Study site personnel and the Sponsor (except for supply chain personnel not involved in decisions regarding subject treatment) will remain blinded.

Available PK and safety data for the sentinel cohort will be reviewed by the IDMC to determine if a dose adjustment should be instituted prior to enrolling the main cohort. Dose reductions or alterations in the escalation paradigm may be recommended to the Sponsor by the IDMC after the sentinel cohort if the drug is not sufficiently tolerated. In addition, dose reductions or escalations may be instituted if the median exposure values for the sentinel cohort lie outside the 5th to 95th percentiles of the simulated reference range across the PK sampling intervals.

The schematic of the study design is presented in Figure 1.

Figure 1: [redacted]

8. STUDY POPULATION

8.1. Inclusion Criteria

To participate in this study, subjects must meet the following criteria:

1. Signed informed consent by the parent(s) or legal representative(s) and, if applicable, assent from developmentally capable pediatric subjects. Consent/assent may be done remotely, if allowed per the site's institutional policy and remote consenting procedures are in place.
2. Diagnosis of EECSWS described by the following criteria:
   - Male and female pediatric subjects aged between 4 and 12 years (inclusive) at screening.
   - Genetic, structural, or unknown origin of EECSWS. Determination of potential genetic origin of EECSWS should be based on prior genetic testing results, if available; however, no genetic testing is required for the determination of study eligibility.
   - SWI >50% during the first hour of overnight NREM sleep based on centralized reading.
   - Focal, multifocal, or generalized spike-and-wave complexes with sleep activation based on investigator assessment and confirmed by central EEG reader.
   - Cognitive stagnation or regression associated with continuous spike-and-wave during sleep (CSWS) as assessed by clinical evaluation.

   Subjects with Landau Kleffner Syndrome are eligible to participate in the study if they meet the above specified diagnostic criteria.
3. Have diagnosis of EECSWS confirmed by the DCP.
4. Subjects of childbearing potential must agree to use highly effective birth control methods consistently while participating in the study until 90 days after the last dose of the study treatment. A female subject of childbearing potential is defined as a subject who has had her first menstrual cycle (ie, menarche). A male subject of childbearing potential is defined as a subject who has reached spermarche.

   Acceptable methods of birth control for female subjects of childbearing potential are:
   - Combined (estrogen and progestogen containing) hormonal contraception or progestogen-only hormonal contraception associated with the inhibition of ovulation used with an effective nonhormonal method of contraception (eg, barrier contraception used with spermicide)
   - Intrauterine hormone-releasing system (IUS) used with an effective nonhormonal method of contraception (eg, barrier contraception used with spermicide)
   - Intrauterine device (IUD)
   - Bilateral tubal occlusion

- Vasectomized partner
- True abstinence from sexual intercourse as the preferred and usual lifestyle. Note that periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Female subjects of childbearing potential must have a negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test result at screening and a negative urine pregnancy test at Day 1.

The acceptable method of contraception for male subjects of childbearing potential is condom with spermicide (cream, spray, foam, gel, suppository, or polymer film).

5. Stable dosage and stable time of intake of at least 1 and up to 3 ASMs, excluding pulse therapies such as systemic corticosteroids and intravenous immunoglobulin (IVIG), from 4 weeks prior to screening and anticipated to be stable from screening until end of study (EOS). Vagal nerve stimulator (VNS) and ketogenic diet are not counted as ASMs.
6. Treatment other than ASMs (excluding pulse therapies such as systemic corticosteroids and IVIG) must be at a stable dosage from 2 weeks prior to screening and anticipated to be stable from screening until EOS.
7. The subject, if using a VNS, must have had the VNS placed at least 3 months prior to screening with stable settings for ≥1 month; settings must remain stable throughout the duration of the study.

8.2. Exclusion Criteria

Subjects will be excluded from the study if they:

1. Are females who are pregnant or currently breastfeeding.
2. Lennox-Gastaut syndrome, Doose syndrome (epilepsy with myoclonic-atonic seizures), or Dravet syndrome.
3. Have a history of neurodegenerative disorders.
4. Presence of a relevant psychiatric disease interfering with cognitive or behavioral functioning (eg, depression, schizophrenia, autism spectrum disorders) unless associated with the EECSWS diagnosis as assessed by the investigator.
5. Presence of relevant neurological disorders other than EECSWS and its underlying conditions as judged by the investigator. Symptomatic conditions underlying EECSWS (eg, neonatal strokes) have to be stable for at least 1 year prior to screening.
6. Life expectancy <12 months due to any concomitant disease.
7. Body weight <10 kg at randomization.
8. Had a medically significant illness within 30 days before Day 1.
9. Have a medically significant abnormality, physical or neurological examination finding, or any other measurements, other than those associated with EECSWS and its underlying conditions, observed during screening or Day 1.

10. Clinically relevant findings in systolic blood pressure (SBP), diastolic blood pressure (DBP), or pulse rate at screening or Day 1 as determined by the investigator.
11. Have an average triplicate ECG corrected QT interval using Fridericia's formula (QTcF) >450 msec or presence of any significant cardiac abnormality at screening.
12. Clinically relevant findings in clinical laboratory tests (hematology, clinical chemistry including thyroid function parameters, and urinalysis) at screening as determined by the investigator.
13. Have aspartate aminotransferase (AST), alanine aminotransferase (ALT), or gamma-glutamyl transferase (GGT) levels >2 × the upper limit of normal (ULN) at screening.
14. Have mild to severe renal impairment as determined by the investigator.
15. Have a history of tonic seizures during sleep.
16. Significant eye disease at screening, which in the opinion of the investigator would affect the subject's ability to safely participate in the study, or findings that would preclude ophthalmic safety examinations.
17. Have received any prohibited medication within 30 days before screening (Section 9.7.1).
18. Have taken cannabinoids, excluding Epidiolex®/Epidyolex®, within 30 days of screening.
19. Pulse therapy such as systemic corticosteroids and IVIG are prohibited for at least 8 weeks prior to screening.
20. [redacted]
21. Have a known or suspected diagnosis of Acquired Immune Deficiency Syndrome (AIDS), or have tested seropositive for human immunodeficiency virus antibody (HIV-Ab) or antigen at screening.
22. Tested positive at screening for hepatitis B surface antigen (HBsAg) or hepatitis C virus antibody (HCV-Ab) with confirmatory positive nucleic acid amplification reflex test.
23. Planned surgical intervention related to structural abnormalities of the brain from screening through the duration of the study.
24. Have a significant risk of suicidal or violent behavior. Subjects will be excluded if they have:
    - Any lifetime history of suicidal behavior *or*
    - Any lifetime history of 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 Columbia-Suicide Severity Rating Scale (C-SSRS), or based on clinical impression for younger subjects.
25. Known intolerance or hypersensitivity to NBI-827104, selective T-type calcium channel blockers, or to any of the excipients of the minitablet.

26. Have received any other investigational drug within 30 days or 5 half-lives (if known), whichever is longer, of Day 1 or plan to use an investigational drug (other than the study treatment) during the study.
27. Any circumstances or conditions, which, in the opinion of the investigator, may affect participation in the study or compliance with the protocol.

8.3. Subject Identification and Replacement of Subjects

Subjects will be identified by their unique Subject identification (ID) number. The subject ID will be noted on electronic case report forms (eCRFs), all source documentation, laboratory documents, and ECG tracings. Subjects who discontinue from the study will not be replaced.

8.4. Randomization

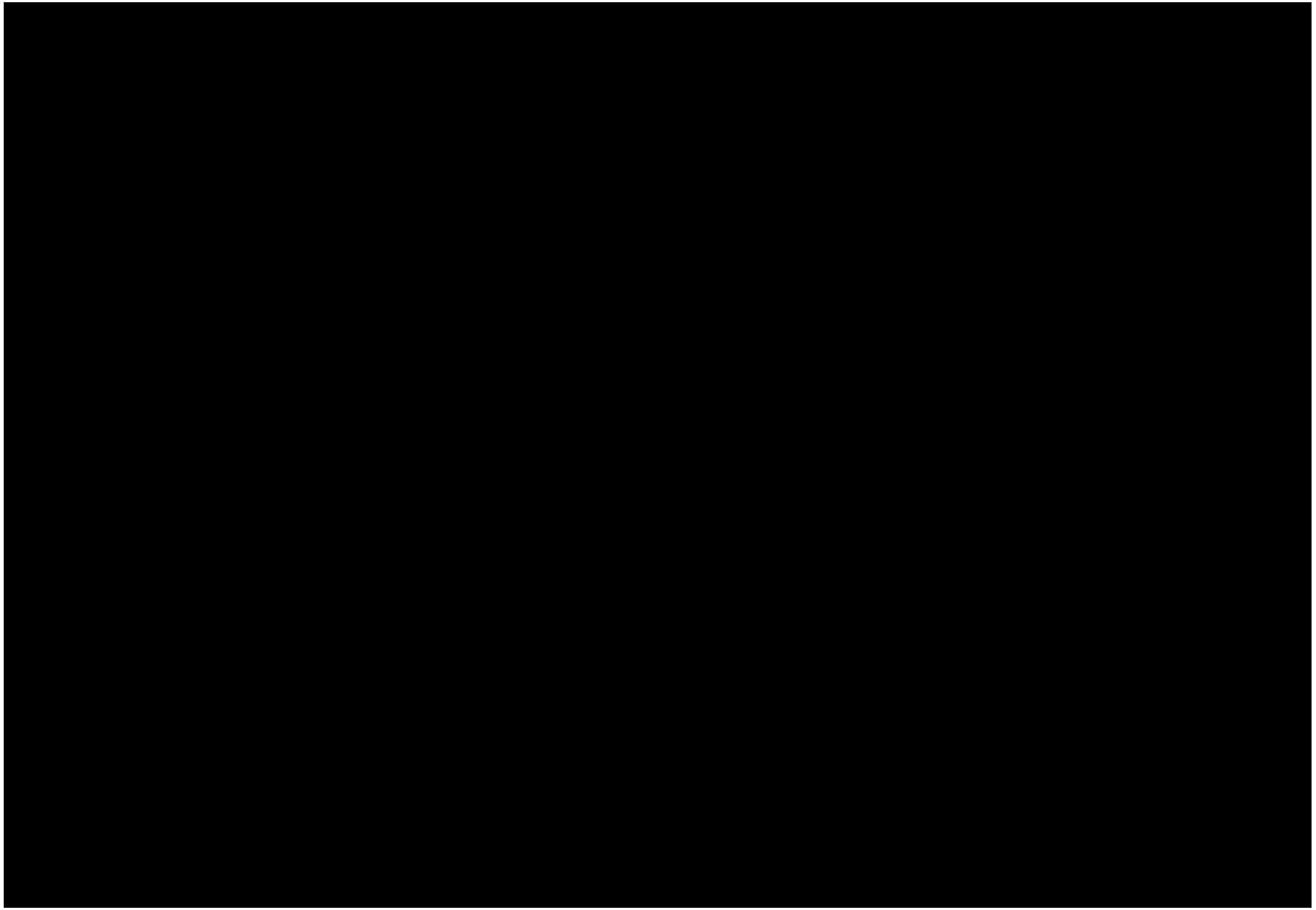
On Day 1, eligible subjects will return to the study center for collection of baseline safety and efficacy assessments. Subjects who continue to be eligible for the study will then be randomized to NBI-827104 or placebo. The first 6 subjects (randomized 2:1; ie, 4 subjects randomized to NBI-827104 and 2 subjects randomized to placebo) will be enrolled into a sentinel cohort for the analysis and review of safety, tolerability, and PK data through [redacted] by an IDMC, before proceeding with enrollment of the remaining 18 subjects in the main cohort (randomized 2:1 [NBI-827104:placebo]).

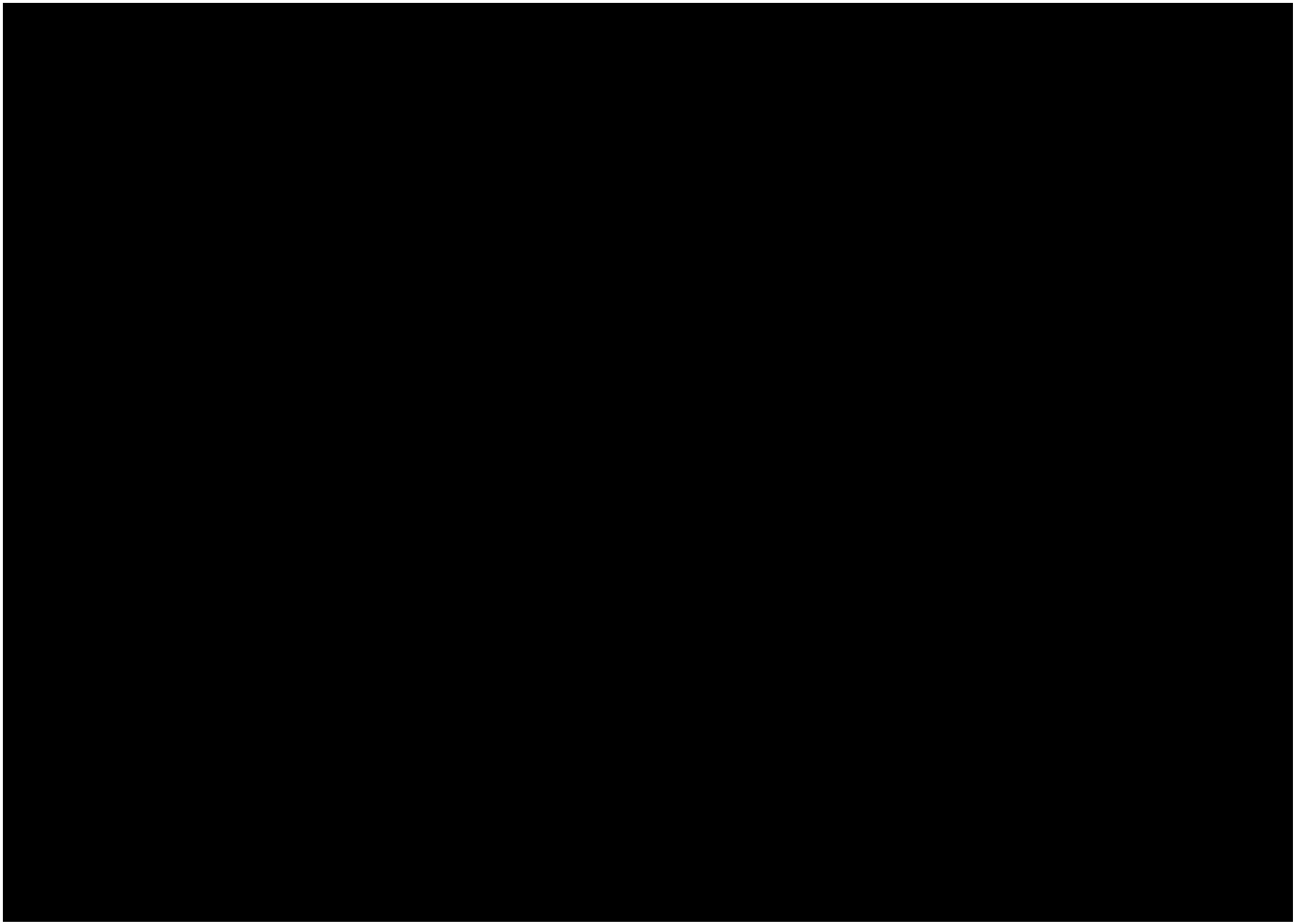
9. STUDY EVALUATIONS

9.1. Schedule of Assessments

A schedule of assessments is shown in Table 2. All study visits after Day 1 will have a visit window of ±3 days. Visits will be the beginning of the week for [redacted] and the end of the week for [redacted]. Informed consent by the parent(s) or legal representative(s) and, if applicable, pediatric assent from developmentally capable pediatric subjects must be collected before any study-related procedures are performed. Consent/assent may be done remotely, if allowed per the site's institutional policy 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.

Table 2: Schedule of Assessments





9.2. Efficacy Assessments

9.2.1. Overnight Video-Electroencephalogram

Inpatient overnight video-EEG using a standard international 10/20 EEG recording setup and concurrent video will be conducted at screening and the end of [redacted], or early termination for subjects who discontinue before the end of [redacted].

The overnight video-EEG recording will be centrally read and used to compute the endpoints on epileptic activity (eg, [redacted] As an outcome measure of this study to quantify electrographic CSWS activity, the SWI is defined as the percentage of seconds with ≥1 spike-wave complex(es) during defined periods of overnight NREM sleep (Aeby et al., 2005; Scheltens-de Boer, 2009).

Detailed information on the conduct and analysis of the video-EEG will be provided in the EEG Charter.

9.2.2. [redacted]

[redacted]

9.2.3. [redacted]

[redacted]

9.2.4. Clinical Global Impression of Change

The Clinical Global Impression of Change (CGI-C), 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; if possible, the same person should rate the CGI-C at all timepoints. [redacted]

9.2.5. Caregiver Global Impression of Change

The Caregiver Global Impression of Change (Caregiver GI-C), 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 condition 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 caregiver's perspective (Guy, 1976).

A caregiver will rate the scale at the scheduled timepoints; if possible, the same person should rate the Caregiver GI-C at all timepoints. [redacted]

9.2.6. Clinical Global Impression of Severity

The Clinical Global Impression of Severity (CGI-S) 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). [redacted]

9.2.7. [redacted]

[redacted]

9.2.7.1. [redacted]

[redacted]

[redacted]

9.2.7.2. [redacted]

[redacted]

9.2.7.3. [redacted]

[redacted]

9.2.7.4. [redacted]

[redacted]

9.2.7.5. [redacted]

9.2.8. [redacted]

9.2.8.1. [redacted]

[redacted]

9.2.8.2. [redacted]

[redacted]

9.2.8.3. [redacted]

[redacted]

[redacted]

9.2.8.4. [redacted]

9.3. Pharmacokinetic Assessments

Blood samples for determination of plasma concentrations of NBI-827104 and metabolites will be collected [redacted] The blood samples will be processed and stored

according to the procedure as specified in the laboratory manual. Samples will be shipped [redacted] to the central laboratory for analysis.

9.4. Safety Assessments

Concomitant medication use and AEs will be monitored throughout the study as described in Section 9.7.1 and Section 11, 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.

9.4.1. Independent Data Monitoring Committee

Ongoing review of safety and tolerability data and the unblinded analysis of sentinel cohort data (including safety, tolerability, and PK data [PK data will only be assessed at [redacted] will be conducted by the IDMC. The IDMC 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 IDMC charter will describe the responsibilities, meeting frequency and data review procedures for the members to follow.

The first 6 subjects (randomized 2:1; ie, 4 subjects randomized to NBI-827104 and 2 subjects randomized to placebo) will be enrolled into a sentinel cohort for the analysis and review of safety, tolerability, and review of PK data through [redacted] by an IDMC, before proceeding with enrollment of the remaining 18 subjects in the main cohort (randomized 2:1 [NBI-827104:placebo]).

9.4.2. Vital Sign Measurements

Vital sign measurements, including SBP and DBP, pulse 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 non-collection must be documented. Blood pressure and pulse rate will be measured using a calibrated automatic blood pressure cuff after the subject has been supine for at least 5 minutes and after approximately 2 minutes standing, if possible.

Vital sign measurements will be obtained before any scheduled blood sample collection at screening, Day 1 (prior to study treatment administration), and beginning of [redacted] (prior to study treatment administration), [redacted] (prior to study treatment administration), [redacted] (prior to study treatment administration), end of [redacted] (prior to study treatment administration and 3 hours post study treatment administration), [redacted] (prior to study treatment administration), [redacted] (prior to study treatment administration), [redacted] (prior to study treatment administration), [redacted] and [redacted] (or early termination).

9.4.3. Medical History

A medical history will be taken at the screening visit and updated on Day 1 and as needed throughout the study.

9.4.4. Physical and Neurological Examination Including Height/Length and Weight

The complete physical and neurological 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, and neurological system, including assessment of level of consciousness, mental status, motor activity (including strength, tone, coordination, and reflexes), sensory testing, and gait.

A complete physical and neurological examination including weight will be performed at screening, Day 1 and end of [redacted] (or early termination). Height/length will be measured at screening only. Height/length may be optional if the participant is unable to stand. If the investigator is unable to obtain height, the reason for non-collection must be captured in the eCRF. Height and weight will be measured with subjects not wearing shoes.

9.4.5. Electrocardiogram

A standard 12-lead ECG will be recorded in triplicate (at least 1 minute apart and within 15 minutes) after the subject has rested supine for at least 5 minutes. The ECG will be centrally read and the parameters that will be assessed include pulse, PR interval, QRS duration, QT interval, and QTcF (machine readings or calculated). 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.

The 12-lead ECG will be conducted at screening, Day 1 (prior to study treatment administration), and beginning of [redacted] (prior to study treatment administration), [redacted] (prior to study treatment administration), [redacted] (prior to study treatment administration), end of [redacted] (prior to study treatment administration and 3 hours post study treatment administration), [redacted] (prior to study treatment administration), [redacted] and [redacted] (or early termination).

9.4.6. Clinical Laboratory Assessments

All clinical laboratory assessments will be performed by a central laboratory. In addition, a urine pregnancy test will be performed by the study site on Day 1 to confirm subject eligibility. 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: complete blood count including white blood cell (WBC) count with differential, red blood cell (RBC) count, hemoglobin, hematocrit, and platelet count, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), red cell distribution width (RDW), mean platelet volume (MPV).

Clinical Chemistry: sodium, potassium, calcium, magnesium, phosphorus, chloride, blood urea nitrogen, bicarbonate, creatinine, uric acid, albumin, alkaline phosphatase, lactate dehydrogenase, AST, ALT, GGT, creatine kinase, total bilirubin, total cholesterol, triglycerides, total protein, glucose, TSH, T3 (free fraction), and T4 (free fraction).

Urinalysis: specific gravity, nitrite, ketones, protein, urobilinogen, glucose, bilirubin, leukocyte esterase, occult blood, and pH; microscopic examination of sediment will be performed only if the results of the urinalysis dipstick evaluation are positive for nitrite, protein, leukocyte esterase, or blood. Urine samples may be considered optional if the subject is unable to provide urine (eg, participant is in a diaper).

The following additional laboratory tests will be performed:

Serology: Blood will be collected for HIV-Ab, HBsAg, and HCV-Ab and reflex nucleic acid amplification testing (if applicable) at screening.

Drug screen: Blood will be collected at screening for a cannabinoid drug testing. A urine cannabinoid drug test may be performed if blood test results are not available prior to randomization at Day 1.

Pregnancy Test: Pregnancy tests will be performed for female subjects of childbearing potential. A serum (β-hCG) pregnancy test will be performed at screening and a urine pregnancy test will be performed on Day 1 and end of [redacted] using a urine pregnancy kit provided by the central laboratory. A serum pregnancy test may be performed if it is not possible to obtain urine.

9.4.7. Estimated Total Blood Sample Volume

The estimated total blood sample volume for each subject is presented in Table 3. These estimates include samples to be collected during screening, the treatment periods, and the final visit (or upon early termination).

Table 3: [redacted]

[redacted]

9.4.8. Columbia-Suicide Severity Rating Scale Children's Versions

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 (Children's Baseline version) and at baseline and visits throughout the study (Children's 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 Children's Version will be administered to subjects ≥6 years of age at screening. Younger subjects or subjects with developmental impairment for whom the C-SSRS would be inappropriate will be monitored for suicidality based on clinical impression.

Subjects with any lifetime suicidal behavior or lifetime 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 should be excluded (see exclusion criterion #24).

The C-SSRS will be administered and scored by the investigator or qualified study center personnel at screening, Day 1, beginning of [redacted] and end of [redacted] (or early termination).

9.4.9. Ophthalmic Examination

An age-appropriate ophthalmic examination will be performed consisting of visual acuity, pupillary light reflex, retinoscopy, as well as slit lamp microscopy testing (following pupillary dilation, and if cooperation can be achieved).

Clinically relevant findings occurring after informed consent and meeting the definition of an AE (new AE or worsening of a previously existing condition) must be recorded on an AE page of the eCRF.

Ophthalmic examinations will be performed at screening, and end of weeks [redacted] (or early termination) and may be performed within 7 days of the scheduled visit.

9.5. Specific Study Period Information

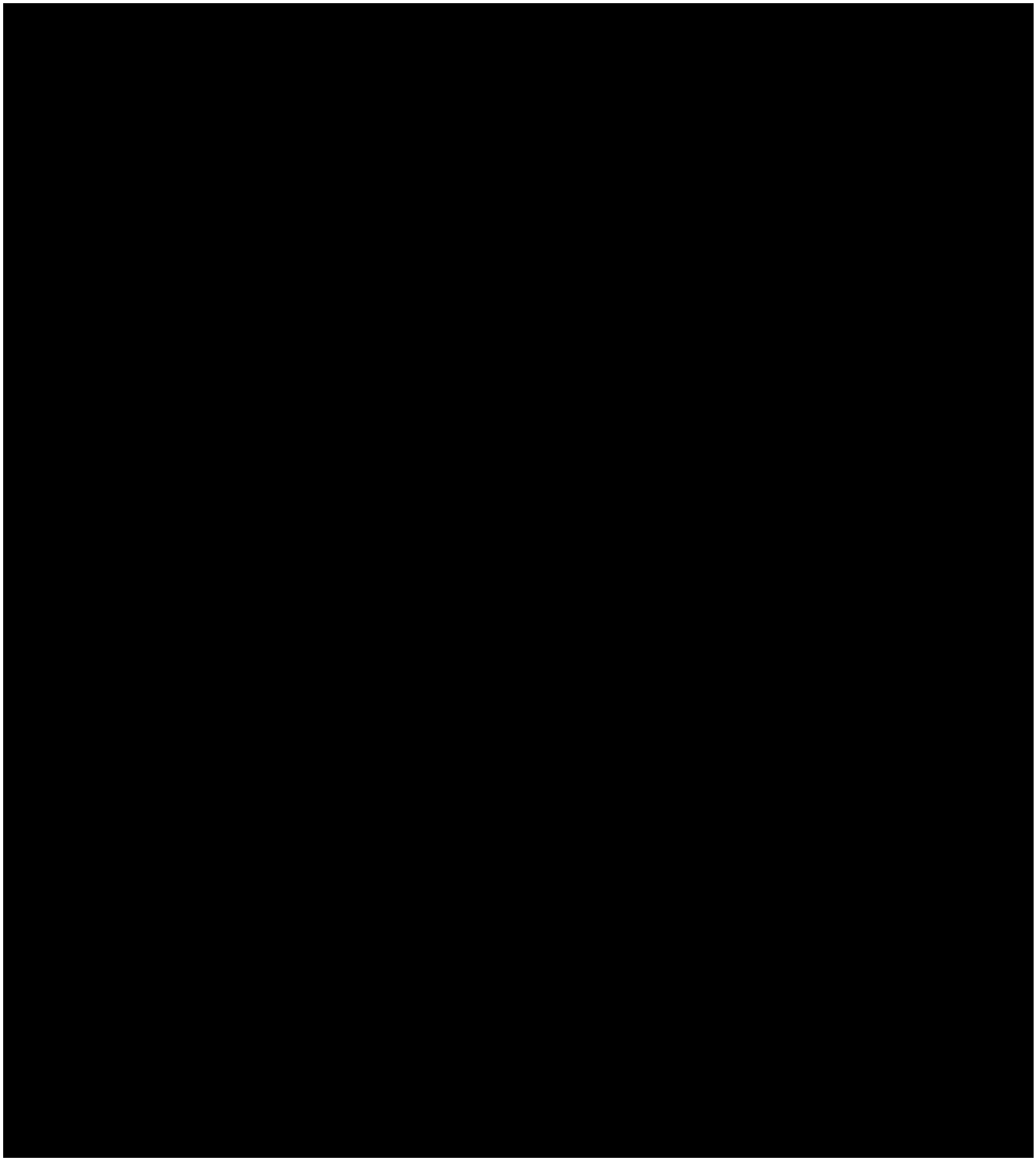
Study visits during the maintenance period may be conducted remotely if individual in-person study visits at the study site are not possible due to Corona Virus Disease 2019 (COVID 19) related reasons (eg, subject is not able to travel to the site for safety reasons or as part of public health measures). In this situation, study treatment may be shipped directly to a subject (Section 10.4). If any study visits during the maintenance period required to be conducted at the site are conducted via telephone or a tele-health platform, this will be documented in the source. Assessments at these visits that must be conducted at the site (eg, overnight video-EEG) may be rescheduled. Any visit assessments that are missed or conducted outside the visit window will be recorded as COVID-19 related protocol deviations.

Assessments for each study visit are not required to be conducted in the order listed in the following sections but should be scheduled to minimize subject fatigue and interference with the subject's ability to sleep during the video-EEG, for study visits with an overnight video-EEG.

9.5.1. Screening (Days -28 to -1)

After signed informed consent by the parent(s) or legal representative(s) and, if applicable, pediatric assent from developmentally capable pediatric subjects is/are obtained, subjects will undergo screening procedures between Day -28 and Day -1.

During screening, the following study evaluations and tasks will be performed at the study center:



9.5.1.1. Diagnosis Confirmation Panel

An external DCP will review and confirm that the subject meets the clinical diagnosis of EECSWS to determine study eligibility prior to randomization on Day 1. Medical history information, as well as any further medical information supporting the diagnosis if available (including the screening overnight video-EEG), will be provided to the DCP to review to confirm the diagnosis. A DCP charter will describe the responsibilities and data review procedures.

9.5.2. Titration Period

9.5.2.1. [redacted]

[redacted]

[redacted]

9.5.2.2. [redacted]

[redacted]

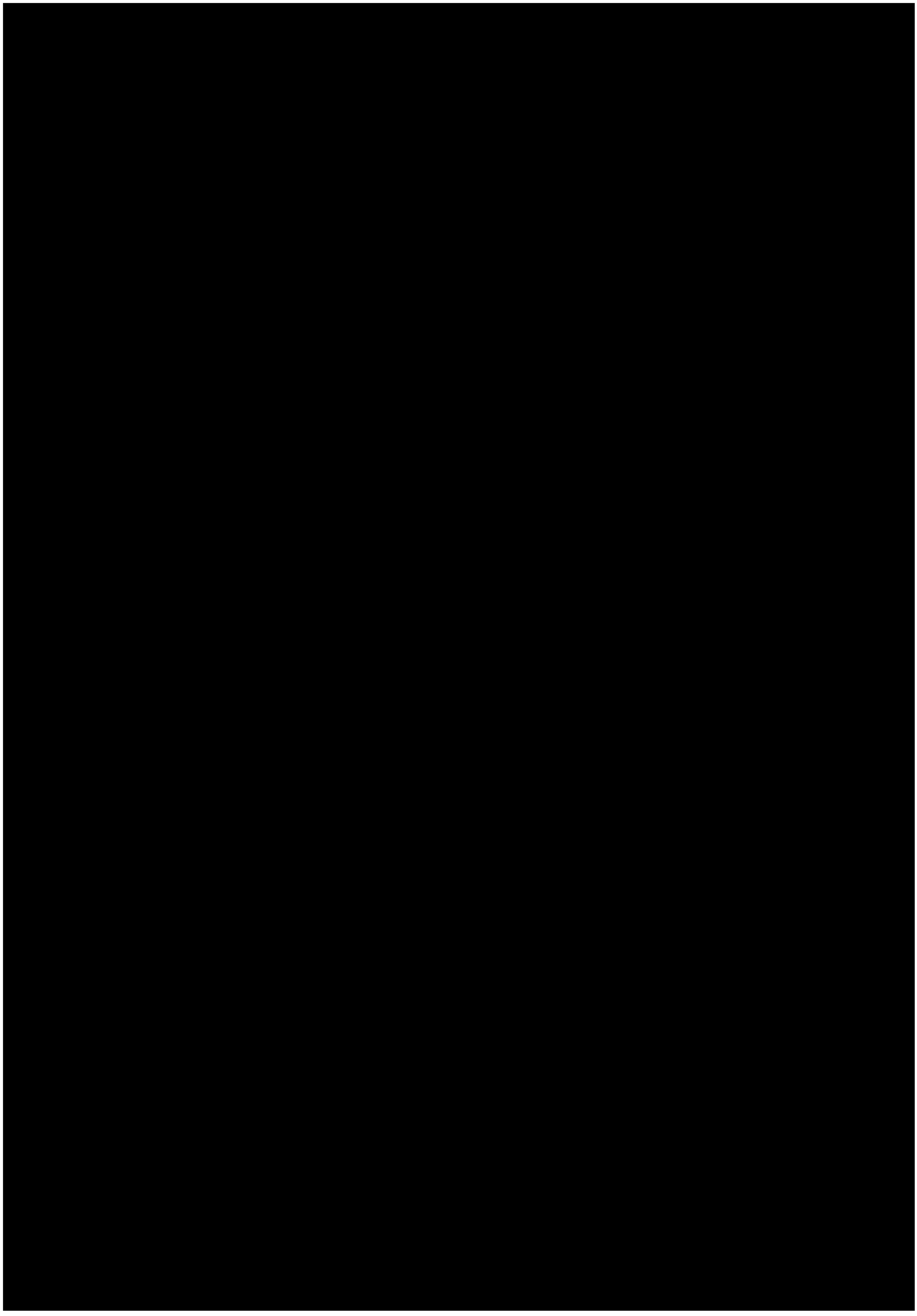
9.5.3. Maintenance Period

9.5.3.1. [redacted]

[redacted]

9.5.3.2. [redacted]

[redacted]



[redacted]

9.5.3.3. [redacted]

[redacted]

9.5.4. Taper Period - [redacted]

[redacted]

9.5.5. Posttreatment End of Study – [redacted]

[redacted]

9.6. Study Duration

The expected duration of study participation for subjects who do not enroll directly into an OLE study is up to [redacted], including up to [redacted] of screening, up to [redacted] of study treatment, and a posttreatment safety period of [redacted]. The expected duration of study participation for subjects who enroll directly into an OLE study is up to [redacted], including up to [redacted] of screening and up to [redacted] of study treatment.

9.7. Prohibitions and Restrictions

9.7.1. 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.

The following medications are allowed:

- Stable background treatment (ie, no dose changes from [redacted] prior to screening and no changes anticipated during the study) with at least 1 and up to 3 concomitant ASMs and/or ketogenic diet/modified Atkins diet. Epidiolex/Epidyolex is allowed and will be considered an ASM. Felbamate is allowed if the subject has been receiving the drug for at least 1 year prior to screening with no safety concerns. During the study duration, subjects will receive the ASMs according to their regular administration schedule. Vagal nerve stimulator (VNS) and ketogenic diet are not counted as ASMs.
- Supportive non-ASM specific therapies (eg, methylphenidate) on stable dose from 2 weeks prior to screening and no changes anticipated during the study.
- Standard of care medication or medication to treat AEs not mentioned as a prohibited concomitant medication.

The following medications are prohibited beginning 30 days before screening until the final study visit (or early termination):

- [redacted]
- Cannabinoids except Epidiolex/Epidyolex.

Pulse therapies such as systemic corticosteroids and IVIG are prohibited for at least 8 weeks prior to screening until the final study visit (or early termination). Other chronic use of steroids, with the exception of steroid replacement therapy, must be approved by the Sponsor.

9.7.2. Dietary Restrictions

[redacted]

9.7.3. Other Restrictions

Subjects will be confined to the study center for 3 overnight stays (screening, [redacted] visit [approximately 24 hours], and [redacted] visit). Subjects will be discharged from the study center after completion of study assessments in the morning after overnight stays.

Participation in another investigational drug study is prohibited for at least 30 days after the last dose of study treatment or 30 days after study completion, whichever is longer.

9.8. Discontinuation of Study Treatment and Subject Withdrawal

Subjects/caregivers 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 if a subject/caregiver requests study treatment dosing to be discontinued or to be withdrawn from the study, respectively. All subjects prematurely discontinuing study treatment dosing should continue study participation to be followed for safety and efficacy outcomes.

9.8.1. Discontinuation of Study Treatment Dosing

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 in the study. The investigator, subject's parent/legal guardian, and subject should discuss a plan for continued participation. Data for any outcome measures, particularly the primary endpoint, as well as safety follow-up, are important to collect. For any subsequent study visits after study treatment is prematurely discontinued, subjects will not be required to undergo PK sampling. Additional study visits and assessments for participants who discontinue study treatment but agree to remain in the study may be conducted remotely. If medically indicated, treatment with medication listed under Section 9.7.1 is 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, despite attempts to decrease the dose.
- If the subject is unable to tolerate the lowest allowable study dose (ie, dose level 1).
- QTcF value >500 msec (cardiologist verified) on any ECG tracing.
- 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, or in the opinion of the investigator.
- Subject is confirmed to be pregnant.
- Subject has any clinically significant treatment-emergent ophthalmic finding.
- Subject has any clinically significant treatment-emergent thyroid function test abnormality (TSH, T3 [free fraction], and T4 [free fraction]).

The investigator or the Sponsor may discontinue study treatment dosing for other reasons including those described below.

- Subject develops a clinically significant laboratory (eg, ALT or AST ≥2.5 times ULN) or ECG abnormality.
- Subject requires a medication that is prohibited by the protocol.

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 and neurological examination, ECG finding, or ophthalmic evaluation. In any case, every effort must be made to undertake safety follow-up procedures.

9.8.2. 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.

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

- Withdrawal by the subject
- Adverse Event
- Death
- Lost to follow-up
- Site terminated by Sponsor
- Study terminated by Sponsor

- Protocol deviation
- Investigator decision

9.8.3. Sponsor's Termination or Pause of Study

The Sponsor reserves the right to discontinue or pause the study overall or at the level of individual sites at any time for clinical or administrative reasons. Study termination must be implemented by the investigator, if instructed to do so by the Sponsor in a time frame that is compatible with the subjects' well-being.

10. STUDY TREATMENT

10.1. Study Treatment Supplies

10.1.1. NBI-827104

The Sponsor or its designee will provide the study center with a supply of NBI-827104 minitablets sufficient for the completion of the treatment period of the study.

10.1.2. Placebo/Reference Drug

The Study Sponsor or its designee will provide the study center with a supply of matching placebo minitablets sufficient for the completion of the treatment period of the study.

10.2. Study Treatment Storage

Formulated NBI-827104 and placebo minitablets [redacted]

The investigator should refer to the label of the study treatment for information on the storage conditions.

Study treatment should be stored and inventoried according to applicable local and federal regulations and study procedures.

10.3. Study Treatment Packaging and Labeling

Each bottle of NBI-827104 or matching placebo will be supplied with a minitablet dispensing device. Instructions on use of the device for dosing will be provided in the Pharmacy Manual. Study treatment will be labeled to comply with the applicable laws and regulations of the countries in which the study sites are located.

10.4. 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.

10.5. Blinding

This study includes up to [redacted] of double-blind, placebo-controlled treatment during which the subject, investigator, and all study center personnel will be blinded to the subject's treatment. The Sponsor will be blinded except for supply chain personnel who are not involved in decisions regarding subject treatment. During this treatment period, all subjects will receive NBI-827104 or placebo to be self-administered once daily.

The randomization code will be broken for an individual subject only if the subject is pregnant, experiences an 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 for unblinding the randomized treatment assignment using an Interactive Web Response System. It is recommended that the investigator contact the Study Medical Monitor (or designee) before unblinding if it would not result in unnecessary delay to the immediate medical management of the subject. Documentation of the unblinding must be maintained.

Members of the IDMC and individuals who generate the IDMC reports and the independent vendor providing the PK analysis will be unblinded throughout the study.

10.6. Study Treatment Preparation and Administration

NBI-827104 will be provided as minitablets [redacted]

10.7. Study Treatment Compliance and Accountability

Subjects/caregivers will bring all unused study treatment and empty drug 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 weighing the container with the minitablets 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.

10.8. Study Treatment Return

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 state and federal regulations and study procedures.

11. 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 ICF has been signed until the subject's final study visit (or upon early termination).

11.1. 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: (1) a worsening or change in nature, severity, or frequency of conditions present at the start of the study; (2) subject deterioration beyond what would be expected due to primary illness; (3) intercurrent illness; and (4) 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
- Seizures will not be considered AEs unless there is a significant increase in seizure frequency, there is a new seizure type, occurrence of status epilepticus, and/or in the investigator's opinion it should be captured as an AE.
- Treatment failure or lack of efficacy

- Pregnancy
- Overdose of either study treatment or concomitant medication without any clinical signs or symptoms.

11.1.1. Intensity of Adverse Events

AEs must be graded for intensity. An intensity category of mild, moderate, or severe, as defined in Table 4, 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 4: 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.

11.1.2. Relationship to Study treatment

The investigator will document his/her opinion of the relationship of the AE to treatment with study treatment using the criteria outlined in Table 5. 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 5: Relationship of Adverse Events to Study treatment

Relationship	Description
Definite	A reaction that follows a reasonable temporal sequence from administration of the drug or in which the drug level has been established in body fluids or tissue; that follows a known or expected response pattern to the suspected drug; and that is confirmed by improvement on stopping or reducing the dosage of the drug, and reappearance of the reaction on repeated exposure.
Possible	An adverse event in which there is reasonable possibility that the drug caused the event. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the adverse event.
Unlikely	A reaction that follows a reasonable temporal sequence from administration of the drug; that follows a known or suspected response pattern to the suspected drug; but that could reasonably be explained by known characteristics of the subject's clinical state.
Not Related	Any event that does not meet the above criteria.

11.2. 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 the Sponsor or its designee:

- SAE, including death
- 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.

11.3. Poststudy Follow-Up of Adverse Events

All AEs, including clinically significant changes in ECGs, physical and neurological 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 or resolves or until 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.

11.4. Serious Adverse Events

All SAEs will be recorded from the time the ICF has been signed 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 11.4.3.

11.4.1. 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.

11.4.2. 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 or designee (and the IRB/IEC, if necessary) immediately (within 24 hours) of the SAE and the outcome of the SAE.

11.4.3. Reporting Serious Adverse Events and Other Immediately Reportable Events

SAEs and other immediately reportable events (defined in Section 11.2) must be reported within 24 hours of first knowledge of the event by study personnel to the Sponsor (contact information provided on the respective forms). 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 Drug Safety and Pharmacovigilance (DSPV) (Table 6). Treatment unblinding and events of suicidal behavior or suicidal ideation type 4 or 5 based on the C-SSRS (or based on clinical impression for subjects under 6 years) should be reported to the Study Medical Monitor.

Table 6: Contact Information for Drug Safety and Pharmacovigilance

Telephone:	[redacted]
Facsimile:	[redacted]
e-mail	[redacted]
Study Medical Monitor:	[redacted] Email: [redacted] Telephone: [redacted]

11.4.4. Expedited Safety Reports

The Sponsor or its representatives will submit an Expedited Safety Report for any suspected adverse reaction (as defined in Section 11.1.2) 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.

The Sponsor 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.

11.5. Pregnancy

Pregnancy is neither an AE nor an SAE unless the criteria for an SAE are met. However, all pregnancies in female subjects who received NBI-827104 will be followed to assess for congenital anomaly. Subjects of childbearing potential must be counseled at all visits to continue using birth control (see inclusion criterion #4 in Section 8.1) until 90 days after the last dose of study treatment. If at any time between the time the ICF is signed and the last study visit, a subject (or the subject's parent/legal guardian) believes she is pregnant, the subject will be instructed to return to the study center within 24 hours and undergo a serum pregnancy test to confirm pregnancy.

All confirmed pregnancies in subjects who received study treatment must be immediately reported to the Sponsor, followed by fax or email of the pregnancy form. A first trimester ultrasound may be requested for all confirmed pregnancies. Pregnancies in subjects who received NBI-827104 will be followed until resolution (ie, termination [voluntary or spontaneous] or birth).

12. DOCUMENTATION OF DATA

12.1. Case Report Forms

The eCRF data for this study are being collected with an electronic data capture (EDC) system. The EDC system and the study-specific eCRFs will comply with Title 21 CFR Part 11. The documentation related to the validation of the EDC system is available through the EDC vendor, while the validation of the study specific eCRFs will be conducted by the Sponsor 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 eCRF for each subject must be reviewed by the investigator and electronically signed on the appropriate eCRF page(s). This should be done as soon as possible after the subject completes 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 the Sponsor (or designee). The Sponsor 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.

The EDC vendor will provide access to the Sponsor 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 provided via a secure transfer mechanism)

and provided to the investigator at that time as a durable record of the center's eCRF data. Although not required, the investigator may make paper printouts of the data.

All clinical work conducted under this protocol is subject to GCP regulations. This includes an inspection by the Sponsor 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 the Sponsor.

12.2. Data Capture, Review, and Validation

Data entered in the EDC system will be verified against the source data by the Sponsor (or designee). Any discrepancies will be corrected online by authorized study center personnel. 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 the Sponsor 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 the Sponsor.

12.3. Coding Dictionaries

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

13. STATISTICAL AND ANALYTICAL PLAN

13.1. Overview

The analysis plan provided in this protocol represents a brief description of the planned analyses. The comprehensive statistical analysis plan (SAP) will be generated prior to final study database lock. The SAP may include a number of additional analyses and data summaries not described in this protocol.

[redacted].

13.2. Analysis Sets

Four analysis sets are defined:

- Full Analysis Set (FAS)

  This analysis set includes all randomized subjects who took at least one dose of study treatment and have at least one efficacy video-EEG assessment. Subjects will be analyzed according to their randomized treatment group.

- Per-protocol set

  This analysis set includes all randomized subjects who completed at least 6 weeks of treatment without protocol deviations that may affect the evaluation of the primary endpoint. Subjects will be analyzed according to their randomized treatment group. Details regarding the specific protocol deviations or criteria that will exclude subjects from the per-protocol set will be defined in the SAP.

- Safety set

  All subjects who received at least one dose of study treatment in the study will be included in the Safety set. The Safety set is the primary analysis population for safety assessments. Subjects will be analyzed according to the study treatment they received.

- Pharmacokinetic set

  This analysis set comprises all subjects included in the Safety set who had at least one evaluable plasma concentration after initiation of NBI-827104 and did not deviate from the protocol in a way that might affect the evaluation of the PK endpoint. The PK set will be employed in the analysis of the PK parameters.

13.3. Sample Size Determination

The sample size is based on the primary endpoint, expressed as a ratio of SWI at the end of [redacted] to baseline. A ratio to baseline was preferred over an absolute or relative change from baseline, because of the better statistical properties of the former.

The associated summary statistic on a treatment group level is the geometric mean ratio (GMR) to baseline (obtained by exponentiating the mean of the log-transformed ratios). A GMR <1 indicates an improvement from baseline in the treatment group.

The treatment effect is expressed as a ratio of ratios: the GMR in the NBI-827104 group divided by the GMR in the placebo group. [redacted]

These numbers will provide the following power to detect a difference in the primary endpoint between NBI-827104 and placebo at [redacted] (at a two-sided α=0.10) as presented in Table 7.

Table 7: [redacted]

[redacted]

13.4. Handling of Missing Data

All available study data will be included in relevant summaries and data displays, including any available data for subjects with incomplete or missing data. Missing data for the primary efficacy endpoint (ratio of SWI at the end of [redacted] to baseline) will be imputed using last observation carried forward. Any methods of handling missing data in the secondary and other endpoints will be specified in the SAP.

13.5. Disposition of Subjects

A summary of subject disposition will be prepared that displays the number of subjects who were randomized, received study treatment, and completed the study. The number of subjects who did not complete the study will be displayed both overall and by reason for discontinuation.

13.6. Important Protocol Deviations

A summary of the number and percentage of subjects with important protocol deviations by deviation category and by treatment group will be provided for all randomized subjects.

13.7. Demographics and Baseline Subject Characteristics

Age, height/length, weight, body mass index, gender, race, and ethnicity will be summarized with descriptive statistics or frequency tables as appropriate.

13.8. Study Treatment Dosing and Compliance

The average daily dose of study treatment will be summarized using descriptive statistics over the periods corresponding to each dose level (ie, [redacted]) for each body weight category. The cumulative dose of study treatment taken over the entire study period will also be summarized.

The number and percentage of subjects who are dose compliant (at least 80% of expected dose taken) will be summarized with descriptive statistics by visit and for the full treatment period.

13.9. Pharmacokinetic Parameters

PK analyses will be performed using the pharmacokinetic analysis set. PK parameters will be calculated using non-compartmental methods.

[redacted]

13.10. Efficacy Data

Primary efficacy endpoint:

- Ratio of SWI at the end of [redacted] to baseline during the first hour (60 minutes) of NREM sleep based on centralized video-EEG reading, where baseline is defined as the last value measured prior to intake of study treatment on Day 1.

The primary endpoint was selected based on the observation of highest SWI during the first NREM sleep phases compared with the last (Bölsterli Heinzle et al., 2014), as well as demonstrated sensitivity and responsiveness in a retrospective review of video-EEG data collected in a patient population of children with EECSWS (Aeby et al., 2005).

Secondary efficacy endpoints:

- Ratio of SWI at the end of [redacted] to baseline during the first hour (60 minutes) of NREM sleep, based on centralized evaluation.
- Caregiver GI-C and CGI-C scores at the end of [redacted]
- Change from baseline to the end of [redacted] in CGI-S scores.

Exploratory efficacy endpoints:

[redacted]

The primary efficacy analyses will be performed using the FAS. The Per-protocol analysis set will be used for supportive analyses.

13.11. Safety Data

Safety analyses will be performed using the Safety set.

AEs will be summarized (frequency counts and percentages) by system organ class and/or preferred term, and maximum intensity.

Descriptive summary statistics of the observed values and changes from baseline to each scheduled visit in clinical laboratory parameters will be provided. The number (%) of subjects with marked laboratory abnormalities will be tabulated.

Observed values and changes from baseline to each scheduled visit in vital signs (SBP and DBP, pulse rate), ECG parameters (QTcF, HR, PR interval, QRS duration), and C-SSRS will be summarized. The number (%) of subjects with marked ECG abnormalities will be tabulated.

13.12. Sentinel Cohort Analysis

The first 6 subjects (randomized 2:1; ie, 4 subjects randomized to NBI-827104 and 2 subjects randomized to placebo) will be enrolled into a sentinel cohort for the analysis of safety, tolerability, and PK data through [redacted] Efficacy analyses will not be performed as part of this analysis, [redacted]

The unblinded analysis of safety and tolerability data for the sentinel cohort will be conducted by the IDMC. The analysis of the PK data through [redacted] in the sentinel cohort will be conducted by an independent, unblinded vendor; this vendor will provide reports to the Sponsor and the IDMC. Based on the tolerability and exposure data obtained from the sentinel cohort, the IDMC may recommend that doses and/or the escalation paradigm be adjusted to achieve the targeted exposure or improve tolerability. Provisions will be made to ensure all Sponsor personnel remain blinded throughout the study.

14. REGULATORY AND ETHICAL ISSUES

14.1. General Legal References

The study will be carried out according to provisions of the 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.

14.2. 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.

14.3. 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 in accordance with local procedures and regulations.

14.4. Required Documents

The investigator must provide the Sponsor 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 both 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.

14.5. Informed Consent

Parent(s) or legal guardian(s) will provide informed consent with pediatric assent (if developmentally capable of providing assent) before the performance of any study-related procedures. Consent/assent may be done remotely, if allowed per the site's institutional policy and remote consenting procedures are in place.

Each subject's chart will include the signed ICF with pediatric assent for study participation. When the study treatment is completed and the eCRF has been monitored, the ICF and pediatric assent will be kept in the investigator's central study file. Regulatory authorities may check the existence of the signed ICF and the pediatric assent in this central study folder.

14.6. 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.

14.7. Quality Assurance

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

14.8. Record Retention

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

The Sponsor 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, the Sponsor must be informed of the individual who will be assuming this responsibility.

14.9. Confidentiality

The Sponsor 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 the Sponsor; it shall not be disclosed to others without written consent of the Sponsor; 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 the Sponsor as deemed necessary. To allow the use of the information derived from this clinical study and to ensure compliance to current federal regulations, the investigator is obliged to furnish the Sponsor with the complete test results and all data compiled in this study.

14.10. 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.

15. STUDY COMMENCEMENT AND DISCONTINUATION

The Sponsor reserves the right to terminate the study at any time globally or locally. Investigators can terminate the participation of their site in the study at any time.

If a study is suspended or prematurely terminated, the sponsor will promptly inform the investigators, the IECs/IRBs, and health authorities, as appropriate, and provide the reasons for the suspension or termination.

If the study is suspended or prematurely terminated for any reason, the investigator — in agreement with the sponsor — must promptly inform all enrolled subjects and ensure their appropriate treatment and follow-up. The sponsor may inform the investigator of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subjects' interests.

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