Protocol Title:	Long-Term, Open-Label Extension Study to Evaluate the Safety and Tolerability of NBI-827104 in Pediatric Subjects with Epileptic Encephalopathy with Continuous Spike-and-Wave During Sleep
Protocol Identifier:	NBI-827104-CSWS2025
EudraCT:	2021-006788-11
Phase:	Phase 2
Sponsor:	Neurocrine Biosciences, Inc. [redacted] San Diego, CA [redacted] United States
Study Medical Director:	[redacted] Telephone: Cell Phone:
Serious Adverse Event Reporting:	Facsimile: [redacted] Email:
Protocol Amendment	2.0 – 30 March 2023

PROTOCOL AMENDMENTS

Protocol/Amendments	Date
Original Protocol	26 August 2021
Amendment 1.0	29 November 2021
Amendment 1.1	19 April 2022
Amendment 1.2	19 August 2022
Amendment 2.0	30 March 2023

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

β-hCG	β-human chorionic gonadotropin
[redacted]	[redacted]
AE	Adverse event
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine aminotransferase
ASM	Antiseizure medication
AST	Aspartate aminotransferase
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Ca_V	Voltage-gated calcium channel subtype
CFR	Code of Federal Regulations
[redacted]	[redacted]
[redacted]	[redacted]
CI	Confidence interval
[redacted]	[redacted]
CRO	Contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CSWS	Continuous spike-and-wave during sleep
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
DCP	Diagnosis Confirmation Panel
DL	Dose level
DMC	Data Monitoring Committee
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
[redacted]	[redacted]
ESES	Electrical status epilepticus during sleep
ET	Early termination
FOS	Focal onset seizures
GAERS	Genetic absence epilepsy in rats from Strasbourg
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GTCS	Generalized tonic clonic seizure
HBsAg	Hepatitis B surface antigen
HCV-Ab	Hepatitis C virus antibody
HIV-Ab	Human immunodeficiency virus antibody
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IGE	Idiopathic generalized epilepsy
IRB	Institutional Review Board
IVIG	Intravenous immunoglobulin
MedDRA	Medical Dictionary for Regulatory Activities
NBI	Neurocrine Biosciences, Inc.
NOAEL	No observed adverse effect level
NREM	Nonrapid eye movement
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
QTcF	Corrected QT interval using Fridericia's formula
qd	Once a day
REM	Rapid eye movement
SAE	Serious adverse event

SAP	Statistical analysis plan
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
TEAE	Treatment-emergent adverse event
[redacted]	[redacted]
[redacted]	[redacted]
US	United States
[redacted]	[redacted]
VNS	Vagus nerve stimulator
WAG/Rij	Wistar Albino Glaxo from Rijswijk
[redacted]	[redacted]
[redacted]	[redacted]

1. SYNOPSIS

Title of study: Long-Term, Open-Label Extension Study to Evaluate the Safety and Tolerability of NBI-827104 in Pediatric Subjects with Epileptic Encephalopathy with Continuous Spike-and-Wave During Sleep

Protocol number: NBI-827104-CSWS2025

Phase of development: 2

Study center(s): This study will be conducted at approximately 24 study centers in the United States and Europe.

Objectives

Primary:

- To evaluate the long-term safety and tolerability of NBI-827104 in pediatric subjects with epileptic encephalopathy with continuous spike-and-wave during sleep (EECSWS).

[redacted]

Study design:

This is a Phase 2, multicenter, open-label extension, interventional study to evaluate the long-term safety, tolerability, [redacted] effectiveness of NBI-827104 in pediatric subjects with EECSWS. This study will enroll approximately 24 male and female subjects, who were 4 to 12 years of age (inclusive) at the time of enrollment in the Phase 2, multicenter, randomized, double-blind, placebo controlled, parallel-group Study NBI 827104 CSWS2010. These subjects may enroll directly or indirectly into this study, as described below.

- Complete Week 12 of Study NBI-827104-CSWS2010 and enroll directly into the current study. The Week 12 End of Maintenance Visit for Study NBI-827104-CSWS2010 and the Day 1 Visit for the current study will occur at the same visit.
- Complete Week 12, a 1-week dose taper if applicable, and the posttreatment safety period of Study NBI-827104-CSWS2010. A gap between the final visit of Study NBI-827104-CSWS2010 and the current study is allowed. These subjects are required to undergo screening procedures in the current study.

Subjects who did not participate in Study-NBI 827104-CSWS2010 may enroll if [redacted]; these subjects will be aged 4 to 12 years (inclusive) at the time of enrollment in Study NBI-827104-CSWS2025. Subjects may be eligible to enter the current study if they meet the specified inclusion criteria and none of the exclusion criteria. Subjects who did not participate in Study NBI-827104-CSWS2010 will have their diagnosis confirmed by an external Diagnosis Confirmation Panel (DCP).

Parental or legal guardian informed consent with pediatric assent from developmentally capable subjects must be provided for all subjects. Enrollment of eligible subjects will not be limited based on body weight category or age group.

The study will consist of the following periods:

- Screening Period [redacted]: Applicable only for subjects who do not enroll directly from or did not participate in Study NBI-827104-CSWS2010
- Dose Titration Period [redacted]: Titration from DL 1 to DL 3
- Long-Term Treatment Period [redacted]: Treatment at the highest tolerated dose of the Dose Titration Period, with the potential for up to 2 additional, sequential dose escalations as follows:
  - Long-Term Treatment Period A [redacted]: For subjects who titrate to a maximum of DL 3
  - Long-Term Treatment Period B [redacted]: For subjects who exit Long-Term Treatment Period A to escalate to DL 4
  - Long-Term Treatment Period C [redacted], if applicable: For subjects who exit Long-Term Treatment Period B to escalate to DL 5. Dose escalation to DL 5 will depend on evaluation of safety, tolerability, [redacted] of subjects who escalate to DL 4.
- Dose Taper Period [redacted]
- Safety Follow-Up Period [redacted]

The maximum duration of an individual subject's study participation is up to 242 weeks.

NBI-827104 will be administered orally, once a day (qd), during the Dose Titration, Long-Term Treatment, and Dose Taper Periods, for a maximum treatment duration of 234 weeks. Study visits will occur approximately every [redacted] during the first [redacted] of the study and the first [redacted] after dose escalation to DL 4 and DL 5. Thereafter, study visits will occur every [redacted], with phone calls approximately [redacted] after each study visit. At the end of their final Long-Term Treatment Period (A, B, or C), subjects will begin the Taper Period, followed by the Safety Follow-Up Period.

Screening Period:

For subjects who enroll directly from Study NBI-827104-CSWS2010, informed consent/assent may be provided within 28 days prior to Day 1, or on Day 1 (the same visit as the Week 12 End of Maintenance Visit for Study NBI-827104-CSWS2010). For subjects who do not enroll directly or who did not participate in Study NBI-827104-CSWS2010, informed consent/assent must be provided before screening assessments start. After providing parental or legal guardian informed consent with pediatric assent from developmentally capable subjects, subjects who do not enroll directly from Study NBI-827104-CSWS2010 will be screened to determine eligibility [redacted] before the start of study treatment dosing on Day 1.

Subjects who did not previously participate in Study NBI-827104-CSWS2010 may be permitted to enroll in this study if [redacted].

Dose Titration Period (Dose Level 1 through Dose Level 3):

During the Dose Titration Period, all subjects will start at DL 1 based on body weight category as shown in the table below. The initial weight group assignment will be based on the subject's weight on Day 1. Subjects will receive the initial dose at [redacted] and may increase to [redacted] and [redacted]. Investigator discretion may be used to determine the dose titration schedule based on tolerability, but dose titration should be no faster than once every [redacted], excepting situations where breakthrough seizures or other safety issues are observed. Exceptions to the titration schedule for safety purposes should be discussed with the Medical Monitor. Titration to DLs that a subject did not tolerate in Study NBI-827104-CSWS2010 is permitted but not required. The site will contact the subject's parent(s)/caregiver(s) at the end of each week during the Dose Titration Period to assess tolerability. If

a subject cannot tolerate a dose after dose titration, they can receive the previously tolerated DL and remain at that DL for up to [redacted] in Long-Term Treatment Period A. Subjects who cannot tolerate the lowest allowable dose (ie, DL 1) will discontinue study treatment and be withdrawn from the study.

[redacted]

Long-Term Treatment Periods (A, B, and C):

Subjects who tolerate DL 3 for at least [redacted] will return to the study site as soon as feasible on [redacted] to increase their dose to DL 4 and initiate Long-Term Treatment Period B [redacted]). Subjects who do not tolerate DL 3 or who are otherwise not candidates for dose escalation to DL 4 will continue in Long-Term Treatment Period A [redacted] at their highest tolerated DL (DL 1 to 3) until the [redacted] End of Long-Term Treatment Visit or early termination (ET).

[redacted] If the data support an increase to DL 5, the maximum DL for the study will be increased to DL 5 [redacted]. Thereafter, subjects who have tolerated DL 4 for at least 1 week will return to the study site to escalate to DL 5 and initiate Long-Term Treatment Period C [redacted]. Subjects who did not tolerate DL 4 or who are otherwise not candidates for dose escalation to DL 5 will continue in Long-Term Treatment Period B at their highest tolerated DL (DL 1 to 4) until the [redacted] End of Long-Term Treatment Visit or ET. If the maximum DL for the study is not increased to DL 5, subjects who escalated to DL 4 will continue with Long-Term Treatment Period B at their highest tolerated DL (DL 1 to 4) until the [redacted] End of Long-Term Treatment Visit or ET.

Throughout the Long-Term Treatment Period (A, B, or C), subjects will maintain their highest tolerated dose until the end of study treatment. During Long-Term Treatment Period A, study treatment dose may be increased or decreased by 1 DL [redacted] within the subject's body weight category as needed based on investigator assessment of safety, tolerability, or efficacy, up to DL 3. During Long-Term Treatment Period B or C, if a subject cannot tolerate the dose escalation to DL 4 and 5, respectively, the subject may receive the next lower tolerated DL and should remain at that dose until [redacted]. After [redacted], the dose may be increased or decreased by 1 DL [redacted] within the subject's body weight category as needed based on safety, tolerability, or efficacy, up to the maximum approved DL. A subject's dose may not exceed the allowable maximum dose for their body weight category (see table).

Initiation or adjustments of concomitant ASMs, vagus nerve stimulator (VNS) settings, and/or a ketogenic diet are not allowed for [redacted] of study treatment. Usage of steroids and/or intravenous immunoglobulin (IVIG) are not allowed for [redacted] prior to screening (or Day 1 for subjects who enrolled directly from Study NBI-827104-CSWS2010) and through the first [redacted] of study treatment. After the first [redacted] of study treatment and through

[redacted] (A, B, or C), initiation or adjustment of concomitant ASMs, VNS settings, ketogenic diet, steroids, and/or IVIG will require prior consultation with the Medical Monitor. After [redacted] (A, B, or C), these treatments may be increased, decreased, stopped, or started based on investigator assessment with parent/caregiver input and additional consultation with the Medical Monitor is not required.

Dose Taper Period:

At the end of their final Long-Term Treatment Period (A, B, or C), subjects will enter an up to [redacted] Dose Taper Period to avoid potential withdrawal seizures due to abrupt treatment discontinuation (Marciani et al., 1985). The dose of study treatment will be reduced by 1 DL every [redacted]. Subjects receiving DL 1 or DL 2 at the end of their final Long-Term Treatment Period will not require dose tapering and will enter the Safety Follow-Up Period after completing the Long-Term Treatment Period.

Study Treatment Discontinuation:

Subjects receiving DL 3 or higher who discontinue study treatment at any time before the end of their final Long-Term Treatment Period (A, B, or C) should undergo dose de-escalation if appropriate to avoid potential withdrawal seizures due to abrupt treatment discontinuation. The subject's current dose would be reduced, based on the investigator's judgment and medical urgency, in a stepwise manner over a period of up to [redacted]. Guidance for implementing a more rapid de-escalation will be provided as needed to the investigator by the Medical Monitor on an individual basis based on clinical judgment.

Subjects who prematurely discontinue study treatment should complete ET assessments as soon as feasible, undergo dose de-escalation if appropriate, and have a safety follow-up phone call and visit approximately [redacted] after the last dose of study treatment, respectively (if a subject's last dose of study treatment was [redacted] before the ET Visit, no additional phone call is needed; if a subject's last dose of study treatment was [redacted] before the ET Visit, no additional visit is needed). Subjects who discontinue study treatment will be withdrawn from the study.

Safety Follow-Up Period:

After the last dose of study treatment, subjects will enter a [redacted] Safety Follow-Up Period, which includes a follow-up telephone call approximately [redacted] after the last dose of study treatment and a study visit approximately [redacted] after the last dose of study treatment.

Study population: Up to approximately 24 male and female subjects who meet all of the inclusion and none of the exclusion criteria may participate in this study. Eligible subjects who participated in Study NBI-827104-CSWS2010 aged 4 to 12 years (inclusive) at the time of enrollment in Study NBI-827104-CSWS2010 may enroll directly or indirectly into this study.

Subjects who did not participate in Study-NBI 827104-CSWS2010 may enroll if [redacted]; these new subjects will be aged 4 to 12 years (inclusive) at the time of enrollment in Study NBI-827104-CSWS2025.

Duration of study treatment and study participation: The maximum duration of study participation for each subject is up to approximately 242 weeks, including up to 234 weeks of study treatment.

Investigational product, dosage, and mode of administration: NBI-827104 oral granules for sprinkle will be provided as [redacted] for oral administration to be taken qd [redacted].

Reference therapy, dose, and mode of administration: Not applicable

Endpoints

Primary (Safety):

- The occurrence of serious treatment-emergent adverse events (TEAEs).

[redacted]

Statistical methods:

Summary of safety analyses

Subject incidence of TEAEs, serious TEAEs, TEAEs leading to discontinuation of study treatment, and fatal TEAEs will be summarized by system organ class and preferred term.

Descriptive statistics will be generated for additional safety data, including clinical laboratory analytes (hematology and clinical chemistry, including thyroid function studies), vital signs, body weight, electrocardiogram parameters, and Children's C-SSRS.

[redacted]

Plasma NBI-827104 concentrations will be summarized by DL and timepoint overall and by body weight category using arithmetic mean, minimum (min), median, maximum (max), SD, standard error (SE), and two-sided 95% CI of the mean.

[redacted]

2. INTRODUCTION

2.1. Background

2.1.1. Epileptic Encephalopathy with Continuous Spike-Wave Discharges During Sleep and Idiopathic Generalized Epilepsy

Calcium is an important signal transduction element in neurons and its entry into the cell is tightly regulated by 2 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: voltage-gated calcium channel subtype (Cav)3.1, 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 and Shin, 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 and Zamponi, 2006; Zamponi et al., 2010; Cheong and Shin, 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 and Zamponi, 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 and Mezghrani, 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 corticothalamocortical circuitry involved in absence seizures are considered to contribute also to sleep-potentiated continuous spike-wave discharges observed in epileptic encephalopathy with continuous spike-and-wave during sleep

(EECSWS) (Sánchez Fernández et al., 2012; Singhal and Sullivan, 2014). EECSWS is a spectrum of epileptic conditions (ILAE, 2020) 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 and Sullivan, 2014). The sleep potentiation of epileptiform activity leads to an electroencephalogram (EEG) 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 and Sullivan, 2014; Tassinari et al., 2000; Nickels and Wirrell, 2008). Some have suggested that neuronal loss may occur in EECSWS, explaining both the resolution of seizures and ESES in adolescence but the persistence of cognitive disability (Kessi et al., 2019). This has been supported by magnetic resonance imaging volumetric analysis of neocortical regions and subcortical substructures in patients with Landau-Kleffner syndrome. Such analysis has revealed volumetric reductions in bilateral superior temporal areas, particularly the planum temporale and superior temporal gyrus (Takeoka et al., 2004). 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).

2.1.2. NBI-827104 Clinical Experience

NBI-827104 (formerly ACT-709478) is a novel selective and orally available triple T-type calcium channel blocker.

[redacted] 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 is being developed for the treatment of EECSWS.

Study NBI-827104-CSWS2010 was a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy, safety, tolerability, and PK of NBI-827104 in pediatric subjects with EECSWS reviewed and approved by an external Diagnosis Confirmation Panel (DCP). [redacted] For subjects who enroll directly from Study NBI-827104-CSWS2010 to the current Study NBI-827104-CSWS2025, subjects will have completed 12 weeks of either placebo or NBI-827104 study treatment [redacted] in Study NBI-827104-CSWS2010. For subjects who do not enroll directly, with a gap between the 2 studies, subjects will have completed 12 or 13 weeks of either

placebo or NBI-827104 study treatment [redacted] and a [redacted] posttreatment safety period in Study NBI-827104-CSWS2010.

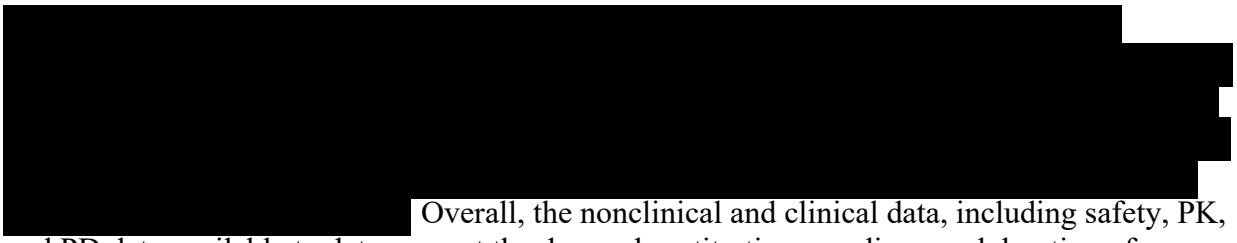
[redacted]

A complete summary of the available clinical and nonclinical data for NBI-827104 is provided in the Investigator's Brochure.

2.2. Benefit/Risk Assessment for NBI-827104 and EECSWS

EECSWS is a spectrum of epileptic conditions (ILAE, 2020) with onset in early childhood and include sleep potentiation of epileptiform activity. The potentiation of epileptiform activity during sleep leads to an EEG pattern of ESES, which consists of continuous spike-waves during NREM 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 and Sullivan, 2014; Tassinari et al., 2000; Nickels and Wirrell, 2008). This has been postulated by some to be secondary to neuronal loss (as suggested by volumetric analysis in certain patients with Landau-Kleffner syndrome) (Kessi et al., 2019; Takeoka et al., 2004). However, the definitive mechanisms underlying the continued neurocognitive regression have not been fully elucidated.

Abnormal T-type calcium channel oscillations have been implicated in the pathophysiology of IGE and spike-wave discharges, in particular. [redacted] Study NBI-827104-CSWS2010 is the first clinical study to evaluate efficacy of NBI-827104 in pediatric subjects with EECSWS, and the current study is an open-label extension of Study NBI-827104-CSWS2010.



Overall, the nonclinical and clinical data, including safety, PK, and PD data available to date support the doses, dose titration paradigm, and duration of treatment in the current study. Further descriptions of nonclinical and clinical safety findings and the reference safety information for NBI-827104 are provided in the current version of the Investigator's Brochure.

ASMs can be associated with potential risks, including cardiovascular effects, central nervous system effects, an increased risk of suicidal thoughts or behavior, and hypersensitivity reactions. The current study includes vital sign assessments and centrally read 12-lead electrocardiograms (ECGs) throughout the study to monitor for cardiovascular abnormalities.

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. 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 [redacted] as noted above. An external, independent Data Monitoring Committee (DMC) will review safety and tolerability data in accordance with the DMC charter throughout the study.

3. OBJECTIVES

3.1. Primary

The primary objective for this study is to evaluate the long-term safety and tolerability of NBI-827104 in pediatric subjects with EECSWS.

3.2. [redacted]

[redacted]

4. STUDY DESIGN

4.1. Overall Study Design

This is a Phase 2, multicenter, open-label extension, interventional study to evaluate the long-term safety, tolerability, [redacted] effectiveness of NBI-827104 in pediatric subjects with EECSWS. This study will enroll approximately 24 male and female subjects, who were 4 to 12 years of age (inclusive) at the time of enrollment in the Phase 2, multicenter, randomized, double-blind, placebo controlled, parallel-group Study NBI 827104 CSWS2010. These subjects may enroll directly or indirectly into this study, as described below.

- Complete Week 12 of Study NBI-827104-CSWS2010 and enroll directly into the current study. The Week 12 End of Maintenance Visit for Study NBI-827104-CSWS2010 and the Day 1 Visit for the current study will occur at the same visit.
- Complete Week 12, a 1-week dose taper if applicable, and the posttreatment safety period of Study NBI-827104-CSWS2010. A gap between the final visit of Study NBI-827104-CSWS2010 and the current study is allowed. These subjects are required to undergo screening procedures in the current study.

Subjects who did not participate in Study-NBI 827104-CSWS2010 may enroll if [redacted]; these subjects

will be aged 4 to 12 years (inclusive) at the time of enrollment in Study NBI-827104-CSWS2025. Subjects may be eligible to enter the current study if they meet the specified inclusion and none of the exclusion criteria. Subjects who did not participate in Study NBI-827104-CSWS2010 will have their diagnosis confirmed by an external DCP.

Parental or legal guardian informed consent with pediatric assent from developmentally capable subjects must be provided for all subjects. Enrollment of eligible subjects will not be limited based on body weight category or age group.

The study will consist of the following periods:

- Screening Period [redacted]: Applicable only for subjects who do not enroll directly from or did not participate in Study NBI-827104-CSWS2010
- Dose Titration Period [redacted]: Titration from DL 1 to DL 3
- Long-Term Treatment Period [redacted]): Treatment at the highest tolerated dose of the Dose Titration Period, with the potential for up to 2 additional, sequential dose escalations as follows:
  - Long-Term Treatment Period A [redacted]: For subjects who titrate to a maximum of DL 3
  - Long-Term Treatment Period B [redacted]: For subjects who exit Long-Term Treatment Period A to escalate to DL 4
  - Long-Term Treatment Period C [redacted], if applicable: For subjects who exit Long-Term Treatment Period B to escalate to DL 5. Dose escalation to DL 5 will depend on evaluation of safety, tolerability, [redacted] of subjects who escalate to DL 4.
- Dose Taper Period [redacted]
- Safety Follow-Up Period [redacted]

The maximum duration of an individual subject's study participation is up to 242 weeks.

NBI-827104 will be administered orally qd during the Dose Titration, Long-Term Treatment, and Dose Taper Periods, for a maximum treatment duration of 234 weeks. Study visits will occur approximately every [redacted] during the first [redacted] of the study and the first [redacted] after dose escalation to DL 4 and DL 5. Thereafter, study visits will occur every [redacted], with phone calls approximately [redacted] after each study visit. At the end of their final Long-Term Treatment Period (A, B, or C), subjects will begin the Taper Period, followed by the Safety Follow-Up Period. Study visits are shown Figure 1 and in the Schedules of Assessments in Table 10 and Table 11.

4.1.1. Screening Period

For subjects who enroll directly from Study NBI-827104-CSWS2010, informed consent/assent may be provided within 28 days prior to Day 1, or on Day 1 (the same visit as the Week 12 End of Maintenance Visit for Study NBI-827104-CSWS2010). For subjects who do not enroll directly or who did not participate in Study NBI-827104-CSWS2010, informed consent/assent

must be provided before screening assessments start. After providing parental or legal guardian informed consent with pediatric assent from developmentally capable subjects, subjects who do not enroll directly from Study NBI-827104-CSWS2010 will be screened to determine eligibility [redacted] before the start of study treatment dosing on Day 1.

Subjects who did not previously participate in Study NBI-827104-CSWS2010 may be permitted to enroll in this study if [redacted].

4.1.2. Dose Titration Period (Dose Level 1 through Dose Level 3)

During the Dose Titration Period, all subjects will start at DL 1 based on body weight category shown in Table 1. The initial weight group assignment will be based on the subject's weight on Day 1. Subjects will receive the initial dose at [redacted] and may increase to [redacted] and [redacted]. Investigator discretion may be used to determine the dose titration schedule based on tolerability, but dose titration should be no faster than once every [redacted], excepting situations where breakthrough seizures or other safety issues are observed. Exceptions to the titration schedule for safety purposes should be discussed with the Medical Monitor. Titration to DLs that a subject did not tolerate in Study NBI-827104-CSWS2010 is permitted but not required. The site will contact the subject's parent(s)/caregiver(s) at the end of each week during the Dose Titration Period to assess tolerability. If a subject cannot tolerate a dose after dose titration, they can receive the previously tolerated DL and remain at that DL for up to [redacted] in Long-Term Treatment Period A. Subjects who cannot tolerate the lowest allowable dose (ie, DL 1) will discontinue study treatment and be withdrawn from the study.

4.1.3. Long-Term Treatment Periods (A, B, and C)

Subjects who tolerate DL 3 for at least [redacted] will return to the study site as soon as feasible on [redacted] to increase their dose to DL 4 and initiate Long-Term Treatment Period B [redacted] (Table 11). Subjects who do not tolerate DL 3 or who are otherwise not candidates for dose escalation to DL 4 will continue in Long-Term Treatment Period A [redacted] at their highest tolerated DL (DL 1 to 3) until the [redacted] End of Long-Term Treatment Visit or early termination (ET) (Table 10).

[redacted] If the data support an increase to DL 5, the maximum DL for the study will be increased to DL 5 [redacted] Thereafter, subjects who have tolerated DL 4 for at least 1 week will return to the study site to escalate to DL 5 and initiate Long-Term Treatment Period C [redacted]. Subjects who did not tolerate DL 4 or who are otherwise not candidates for dose escalation to DL 5 will continue in Long-Term Treatment Period B at their highest tolerated DL (DL 1 to 4) until the [redacted] End of Long-Term Treatment Visit or ET. If the maximum DL for the study is not increased to DL 5, subjects who escalated to DL 4 will continue with Long-Term Treatment Period B at their highest tolerated DL (DL 1 to 4) until the [redacted] End of Long-Term Treatment Visit or ET.

Throughout the Long-Term Treatment Period (A, B, or C), subjects will maintain their highest tolerated dose until the end of study treatment. During Long-Term Treatment Period A, study treatment dose may be increased or decreased by 1 DL [redacted] within the subject's body weight category as needed based on investigator assessment of safety, tolerability, or efficacy, up to DL 3. During Long-Term Treatment Period B or C, if a subject cannot tolerate the dose escalation to DL 4 and 5, respectively, the subject may receive the next lower tolerated DL and should remain at that dose until [redacted]. After [redacted], study treatment dose may be increased or decreased by 1 DL [redacted] within the subject's body weight category as needed based on investigator assessment of safety, tolerability, or efficacy, up to DL 4 (Long-Term Treatment Period B) or DL 5 (Long-Term Treatment Period C). A subject's dose may not exceed the allowable maximum dose for their body weight category (Table 1).

It is anticipated that during the course of the study, subjects may change weight groups. Subjects will begin each DL based on their body weight category as shown in the table above; however, once a subject is on a stable dose, an increase in body weight will not automatically trigger a change in dose if a subject changes weight groups. If the investigator determines a dose change is indicated based on safety, tolerability, or efficacy considerations, a subject's dose may be adjusted to an approved DL based on the new weight group.

Table 1: [redacted]

[redacted]

Initiation or adjustments of concomitant ASMs, vagus nerve stimulator (VNS) settings, and/or a ketogenic diet are not allowed for [redacted] of study treatment. Usage of steroids and/or intravenous immunoglobulin (IVIG) are not allowed for [redacted] prior to screening (or Day 1 for subjects who enrolled directly from Study NBI-827104-CSWS2010) and through the first [redacted] of study treatment. After the first [redacted] of study treatment and through [redacted] (A, B, or C), initiation of adjustment of concomitant ASMs, VNS settings, ketogenic diet, steroids, and/or IVIG will require prior consultation with the Medical Monitor. After [redacted] (A, B, or C), these treatments may be increased, decreased, stopped, or started based on investigator assessment with parent/caregiver input and additional consultation with the Medical Monitor is not required.

4.1.4. Dose Taper Period

At the end of their final Long-Term Treatment Period (A, B, or C), subjects will enter an up to [redacted] Dose Taper Period to avoid potential withdrawal seizures due to abrupt treatment discontinuation (Marciani et al., 1985). The dose of study treatment will be reduced by 1 DL

every [redacted]. Subjects receiving DL 1 or DL 2 at the end of their final Long-Term Treatment Period will not require dose tapering and will enter the Safety Follow-Up Period after completing the Long-Term Treatment Period. The dose taper procedure is described in Section 9.4.3.

4.1.5. Study Treatment Discontinuation

Subjects receiving DL 3 or higher who discontinue study treatment at any time before the end of their final Long-Term Treatment Period (A, B, or C) should undergo dose de-escalation if appropriate to avoid potential withdrawal seizures due to abrupt treatment discontinuation. The subject's current dose would be reduced, based on the investigator's judgment and medical urgency, in a stepwise manner over a period of up to [redacted]. Guidance for implementing a more rapid de-escalation will be provided as needed to the investigator by the Medical Monitor on an individual basis based on clinical judgment.

Subjects who prematurely discontinue study treatment should complete ET assessments as soon as feasible, and a safety follow-up phone call and visit approximately [redacted] after the last dose of study treatment, respectively (if a subject's last dose of study treatment was [redacted] before the ET Visit, no additional phone call is needed; if a subject's last dose of study treatment was [redacted] before the ET Visit, no additional visit is needed). Subjects who discontinue study treatment will be withdrawn from the study.

4.1.6. Safety Follow-Up Period

After the last dose of study treatment, subjects will enter a [redacted]k Safety Follow-Up Period, which includes a follow-up telephone call approximately [redacted] after the last dose of study treatment and a study visit approximately [redacted] after the last dose of study treatment.

A schematic of the study design is shown in Figure 1. Study assessments and procedures are described in Section 9 and will be performed according to the Schedules of Assessments (Table 10 and Table 11).

4.2. Interim Analysis

The Sponsor will review the safety, tolerability, [redacted] of NBI-827104 DL 4 to determine if the study will continue, with the possibility to increase the maximum dose level to DL 5. Safety, tolerability, [redacted] data will be evaluated as follows:

1. [redacted]
2. [redacted]

An independent DMC (Section 11.6.1) will also review the safety and tolerability [redacted] and make a recommendation to the Sponsor for whether the study may continue per the protocol.

4.3. Rationale for Dose Selection

The available clinical data of NBI-827104 include [redacted] The doses were considered generally well tolerated. The dose titration design was based on Phase 1 clinical experience that an up-titration regimen improves tolerability of NBI-827104.

In Study NBI-827104-CSWS2010, the targeted exposure range (mean area under the plasma concentration versus time curve during a dosing interval [$AUC_{0-\tau}$]) of [redacted] was determined by [redacted] The mean $AUC_{0-\tau}$ in pediatric subjects in Study CSWS2010 [redacted] was below the targeted exposure range and was [redacted]

Therefore, DL 4, and the potential for DL 5, have been added to the current study, [redacted]

The DL 4 doses for the current study (Table 1) were calculated based on [redacted] (see Section 11.6.2).

4.4. End of Study Definition

Primary Completion: The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data used for the primary endpoint(s), whether the study concluded as planned or was terminated early. The planned primary completion date for this study is the date when the last subject has completed their Safety Follow-Up Visit assessments. If the study is terminated early, then the primary completion date will be the date of the last visit for the last subject in the study.

End of Study: The end of study is defined as the date of the last visit of the last subject or last scheduled procedure shown in the Schedule of Assessments for the last subject in the study globally.

Figure 1: [redacted]

5. [redacted]

[redacted]

5.1. [redacted]

[redacted]

5.1.1. [redacted]

[redacted]

[redacted]

5.1.2. [redacted]

[redacted]

5.2.

[redacted]

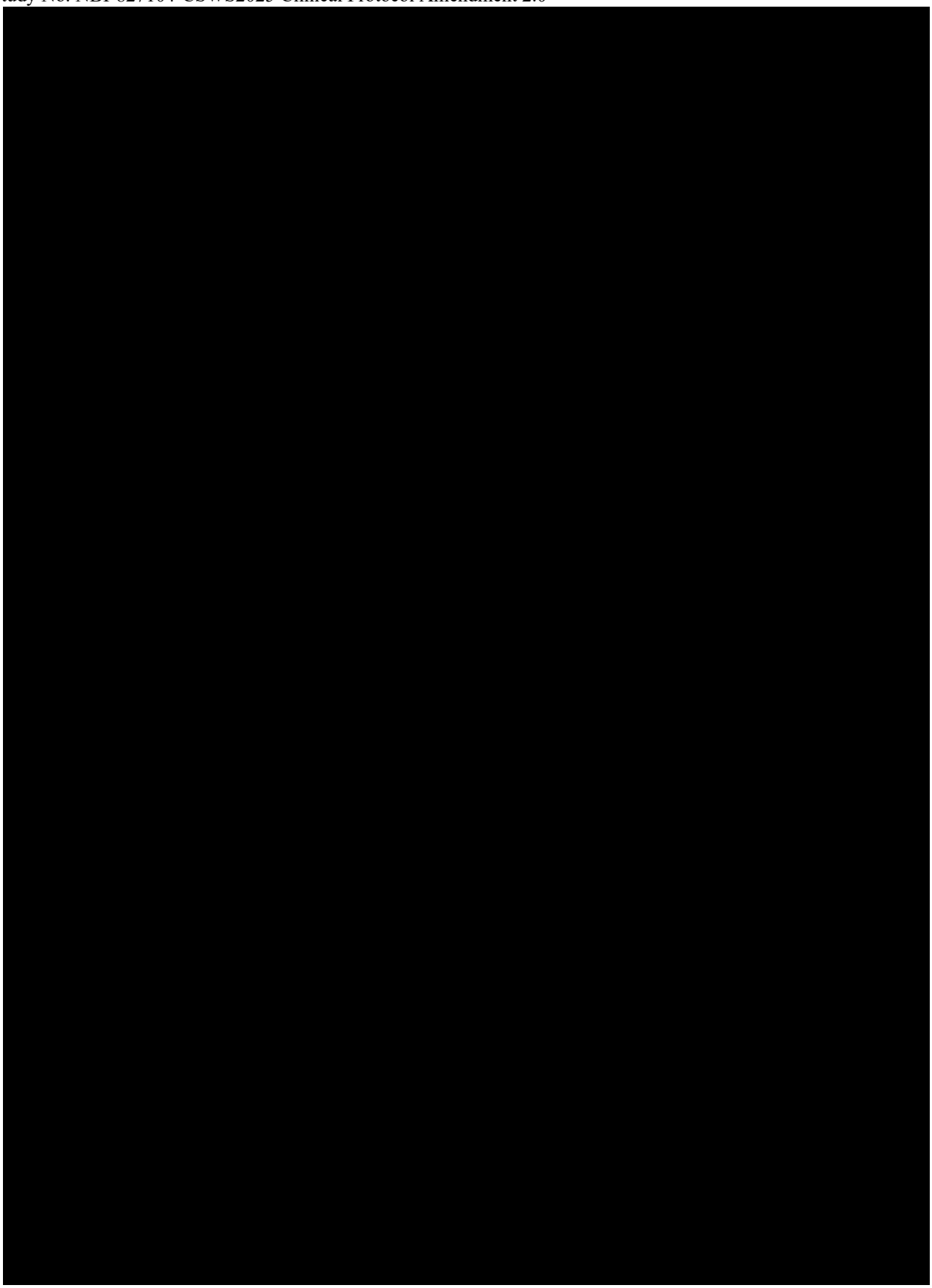
5.2.1.

[redacted]

[redacted]

5.2.2. [redacted]

[redacted]



[redacted]

6. STUDY TREATMENT

6.1. General Information

The study treatment is summarized in Table 2.

Table 2: Study Treatment

Treatment	**Active (NBI-827104)**
Treatment administration	Subjects will receive the initial dose at [redacted] and may increase to [redacted] based on tolerability. Subjects who tolerate DL 3 will increase to DL 4 [redacted] If the maximum dose for the study is increased to DL5, subjects who tolerate DL 4 will increase to DL 5 [redacted] The highest tolerated DL will be maintained through the end of the Long-Term Treatment Period (A, B, or C). Doses should not be adjusted from [redacted] unless the subject is unable to tolerate their current dose. During LT Treatment Period A and after [redacted] in LT Treatment Periods B and C, the dose may be increased or decreased by 1 DL [redacted] within the subject's weight group as needed based on safety, tolerability, or efficacy, up to the maximum approved DL. Subjects will undergo an [redacted] dose taper at the end of their final Long-Term Treatment Period.
Unit dose strength	[redacted]
Dose level	Study treatment doses for each DL are provided for each weight group in Table 1.
Dose formulation	Oral granules for sprinkle (minitablets) for oral administration
Route of administration	Oral
Sourcing	Provided centrally by Sponsor
Packaging and labeling	Study treatment will be provided in [redacted]. Instructions on use of the device for dosing will be provided in the Pharmacy Manual. Each bottle will be labeled in accordance with applicable regulatory requirements.

DL=dose level, LT=Long-Term.

6.2. Study Treatment Administration

NBI-827104 will be provided as [redacted] to be taken [redacted] Further instruction will be provided in the Pharmacy Manual.

Information on dose titration, dose adjustments, dose de-escalation, and dose tapering is provided in Section 4.1.

If a subject forgets or is unable to take the study treatment, the dose should still be taken as long as it is within [redacted] of the usual dosing time; otherwise, the study treatment should be taken at the next dosing time.

6.3. Study Treatment Storage and Compliance

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

6.4. Study Treatment Accountability and Return

Parent(s)/caregiver(s) will bring all unused study treatment and empty packaging material to the center at specified study visits for study treatment 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.

If unused study treatment is not returned to the Sponsor or designee, alternative disposition of study treatment must be documented and follow local laws and regulations.

6.5. Direct-to-Subject Shipments of Study Treatment

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

6.6. Procedures for Overdose

Any dose of NBI-827104 greater than the subject's assigned dose within a 24-hour time period will be considered an overdose.

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

1. Closely monitor the subject for any adverse event (AE)/serious adverse event (SAE) and laboratory abnormalities and follow the AE reporting process. The Study Medical Monitor should be contacted for AEs related to an overdose.
2. Document the total quantity and duration of the excess dose in the electronic Case Report Form (eCRF).

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

7. SUBJECT RESTRICTIONS

7.1. Prior and Concomitant Medications

All prescription and over-the-counter medications, dietary supplements (including vitamins), and herbal supplements taken by the subject within 30 days before screening (for subjects who do not enroll directly from or did not participate in Study NBI-827104-CSWS2010) or Day 1 (for subjects who enroll directly from Study NBI-827104-CSWS2010) will be recorded on the Prior and Concomitant Medications page of the eCRF.

The medications listed in Table 3 are prohibited for the duration indicated.

Table 3: [redacted]

[redacted]

Duration	Prohibited/Restricted Concomitant Medication
Within 30 days prior to screening[a] and during the entire study	[redacted]
	Investigational treatments other than NBI-827104 received in the context of a clinical study, unless approved by the Sponsor.

ACTH=adrenocorticotropic hormone; ASM=antiseizure medication; CYP=cytochrome P450; IVIG=intravenous immunoglobulin; VNS=vagus nerve stimulator.

[a] Durations prior to screening are applicable only to subjects who do not enroll directly from Study NBI-827104-CSWS2010 to the current study or who did not participate in Study NBI-827104-CSWS2010. For subjects who enroll directly from Study NBI-827104-CSWS2010, the start of the duration of the restriction is the start of the subject's participation in this study (ie, Day 1)

Rescue Medicine

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

ASMs

Concomitant ASMs must be stable within [redacted] prior to Day 1 in the Dose Titration Period and through the first [redacted] of study treatment. After the first [redacted] of study treatment and through [redacted] (A, B, or C), initiation or adjustment of concomitant ASMs will require prior consultation with the Medical Monitor. After [redacted] (A, B, or C), concomitant ASMs may be increased, decreased, stopped, or started based on investigator assessment with parent/caregiver input and additional consultation with the Medical Monitor is not required. If ASMs need to be adjusted prior to the first [redacted] of study treatment for safety reasons, these exceptions must be discussed with the Medical Monitor.

7.2. Dietary and Other Restrictions

VNS settings and/or a ketogenic diet must be stable from [redacted] prior to Day 1 (for subjects who do not enroll directly from or participate in Study NBI-827104-CSWS2010) or Day 1 (for subjects who enroll directly from Study NBI-827104-CSWS2010) and through the first [redacted] of study treatment (adjustments are not allowed). After the first [redacted] of study treatment and for the remainder of the study, a ketogenic diet may be started or adjusted and a VNS may be implanted or adjusted.

[redacted] are prohibited from within [redacted] prior to screening (for subjects who do not enroll directly from or participate in Study NBI-827104-CSWS2010) or Day 1 (for subjects who enroll directly from Study NBI-827104-CSWS2010) and until the end of the subject's participation in the study.

[redacted] is prohibited from within [redacted] prior to screening (for subjects who do not enroll directly from or participate in Study NBI-827104-CSWS2010) or Day 1 (for subjects who enroll directly from Study NBI-827104-CSWS2010) and until the end of the subject's participation in the study.

Male subjects of childbearing potential must agree to refrain from donating sperm during the study and for 90 days after the last dose of the study treatment.

8. DISCONTINUATION OF STUDY TREATMENT AND SUBJECT WITHDRAWAL

At any time during the study subjects or their parent(s)/legal guardian(s) can discontinue study treatment or withdraw their consent/assent to participate in the study. The investigator must discontinue study treatment or withdraw any subject from the study at their or their parent(s')/legal guardian(s') request.

8.1. Discontinuation of Study Treatment

If a subject prematurely discontinues study treatment, the investigator will record the reason for discontinuation on the relevant eCRF. Data for any outcome measures, particularly the primary and secondary endpoints, as well as safety follow-up, are important to collect as described in Section 8.2. Subjects receiving DL 3 or higher who discontinue study treatment at any time before the end of long-term treatment should undergo dose de-escalation, if appropriate, as described in Section 9.4.3 .

After a Safety Follow-Up Visit, subjects will be withdrawn from the study.

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

- Withdrawal by subject or parent(s)/legal guardian(s)
- Death
- Lost to follow-up
- Site termination by the Sponsor
- Study termination by the Sponsor
- AE
- Pregnancy
- Lack of efficacy
- Protocol deviation
- Investigator decision
- Sponsor decision

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

- The type, frequency, or severity of any AE becomes unacceptable/intolerable, despite attempts to decrease the DL. This includes AEs of seizures. Criteria for evaluating whether seizures should be considered AEs are provided in Section 10.1.
- The subject is unable to tolerate the lowest allowable dose of study treatment (ie, DL 1).
- QTcF of >500 msec (cardiologist verified) on any ECG tracing.
- The subject is confirmed to be pregnant.
- Withdrawal of consent/assent for study treatment administration by parent(s)/legal guardian(s) or the subject.
- 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 Children's C-SSRS or clinical impression.

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 × the upper limit of normal) or ECG abnormality.
- Subject requires a medication that is prohibited by the protocol.

Every effort should be taken to obtain follow-up data for any subject who discontinues study treatment because of an AE, abnormal laboratory test, vital sign measurement, physical examination, or ECG finding.

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 ET assessments performed as soon as feasible and, unless consent has been withdrawn, will be asked to have a Safety Follow-Up phone call and visit approximately 1 week and 4 weeks after the last dose of study treatment, respectively. If a subject's last dose of study treatment was >1 week before the ET Visit, no additional phone call is needed; if a subject's last dose of study treatment was >4 weeks before the ET Visit, no additional visit is needed.

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

- Withdrawal by the subject or parent(s)/legal guardian(s)
- AE
- Death

- Lost to follow-up
- Site terminated by Sponsor
- Study terminated by Sponsor
- Protocol deviation
- Investigator decision
- Sponsor decision

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

The Sponsor or designee reserves the right to close a study site, terminate or suspend the entire study, or terminate or suspend the study at individual sites, at any time for any reason. If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IRBs/IECs, the regulatory authorities, and any contract research organizations (CROs) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the subject and should assure appropriate therapy and/or follow-up.

9. STUDY ASSESSMENTS AND PROCEDURES

A schedule of assessments is provided in Table 10 and Table 11 (Appendix A). No study procedures should be performed until after signed inform consent is obtained from the parent(s)/legal guardian(s) and pediatric assent from the subject, if applicable (which may be done remotely, if allowed and remote consenting procedures are in place). Subject-related events and activities including specific instructions, procedures, concomitant medications, dispensing of study treatment, and descriptions of AEs should be recorded in the appropriate source documents and eCRFs.

9.1. [redacted]

9.1.1. [redacted]

[redacted]

[redacted]

9.1.2. [redacted]

[redacted]

9.1.3. [redacted]

[redacted]

9.1.4. [redacted]

[redacted]

9.1.5. [redacted]

[redacted]

[redacted]

9.1.6. [redacted]

[redacted]

9.1.6.1. [redacted]

[redacted]

9.1.6.2. [redacted]

[redacted]

9.1.6.3. [redacted]

[redacted]

[redacted]

9.1.6.4. [redacted]

[redacted]

9.1.6.5. [redacted]

[redacted]

9.1.7. [redacted]

[redacted]

9.1.7.1. [redacted]

[redacted]

[redacted]

9.1.7.2. [redacted]

[redacted]

9.1.7.3. [redacted]

[redacted]

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

9.1.8. [redacted]

[redacted]

[redacted]

9.2. [redacted]

[redacted]

9.3. Safety Assessments

Concomitant medication use and AEs will be monitored throughout the study as described in Section 7.1 and Section 10, respectively. Additional safety assessments described in the following sections will be completed at the timepoints specified in the Schedule of Assessments (Table 10 and Table 11).

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.

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.

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

9.3.1. Medical History

For subjects who do not enroll directly from or participate in Study NBI-827104-CSWS2010, a medical history will be taken at the screening visit and updated on Day 1 and as needed throughout the study.

For subjects who enroll directly, a medical history will be taken to update the relevant history from Study NBI-827104-CSWS2010 on Day 1 and as needed throughout the study.

9.3.2. Body Weight

Body weight will be measured at the study visits indicated in the Schedules of Assessments (Table 10 and Table 11). The initial weight group assignment will be based on the subject's weight on Day 1.

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

The complete physical examination will consist of an assessment of general appearance, extremities, skin and mucosae, head, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest, lungs, cardiovascular, abdomen, genito-urinary, musculoskeletal, and neurological system, including assessment of level of consciousness, mental status, muscle strength and tone, coordination and gait, [redacted].

Height/length will be measured with subjects not wearing shoes. Height may be optional if the subject is unable to stand. If the investigator is unable to obtain height/length, the reason for noncollection must be captured in the eCRF. The physical examination schedule is provided in Table 10 and Table 11.

Physical signs of puberty will be assessed using Tanner staging as appropriate based on subject age and stage of puberty as part of the physical examination.

9.3.4. [redacted]

[redacted]

9.3.5. Vital Sign Measurements

Vital signs will be measured for the following: orthostatic systolic and diastolic blood pressure, orthostatic pulse rate, respiratory rate, and body temperature. Orthostatic blood pressures may be considered optional if the subject is unable to stand (eg, subject is in a wheelchair). If the investigator is unable to obtain orthostatic blood pressures, the reason for noncollection must be captured in the eCRF. Blood pressure and pulse rate will be measured 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 prior to study treatment administration on Day 1 or any scheduled blood sample collection, where applicable, at the timepoints specified in the Schedules of Assessments (Table 10 and Table 11).

9.3.6. Electrocardiogram

A standard 12-lead ECG will be recorded after the subject has rested supine for at least 5 minutes. The ECG should be performed in triplicate (at least 1 minute apart and within 15 minutes), if possible. The ECG will be centrally read and parameters that will be assessed include heart rate, 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 will provide a description of the abnormality recorded on the AE eCRF.

The ECG assessment should be performed prior to study treatment administration on Day 1, and prior to any blood sample collection at the timepoints specified in the Schedules of Assessments.

9.3.7. Clinical Laboratory Assessments

All clinical laboratory assessments will be performed by a central laboratory. The central laboratory will provide instructions and supplies to the study staff before study initiation and instructions will be included in a laboratory manual. The following clinical safety laboratory assays will be performed:

Hematology: complete blood count including white blood cell count with differential, red blood cell count, hemoglobin, hematocrit, and platelet count, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, red cell distribution width, and mean platelet volume.

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 protein, glucose, [redacted].

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, subject is in a diaper).

The following additional laboratory test will be performed at screening for subjects who do not enroll directly from or did not participate in Study NBI-827104-CSWS2010:

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

Drug screen: Urine will be collected at screening for cannabinoid drug testing.

Pregnancy test: Pregnancy tests will be performed throughout the study for female subjects of childbearing potential. A serum β-hCG pregnancy test will be performed at screening for subjects who do not enroll directly. A urine pregnancy test (using a urine pregnancy kit provided by the central laboratory) will be performed at the postscreening timepoints indicated in the Schedules of Assessments (Table 10 and Table 11). Female subjects who become of childbearing potential during the study will be required to undergo pregnancy testing at the timepoints indicated in the Schedule of Assessments (Table 10). Serum pregnancy tests should be performed if urine cannot be collected. Any positive urine pregnancy test should be confirmed by a serum pregnancy test.

9.3.8. Estimated Maximum Total Blood Sample Volume

The estimated maximum total blood volume for each subject collected during the study from screening (if applicable) to last visit (Safety Follow-Up Visit) is provided in Table 4.

Based on the blood volumes to be collected at the scheduled study visits, the blood volume collected will not exceed 3% of the total blood volume during a period of 4 weeks and will not exceed 1% at any single time.

Table 4: [redacted]

[redacted]

9.3.9. Columbia-Suicide Severity Rating Scale

The C-SSRS is a validated instrument to prospectively assess suicidal ideation and behavior (http://www.cssrs.columbia.edu). There are versions of the questionnaire designed for use at screening (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 on Day 1. Younger subjects or subjects with developmental impairment for whom the C-SSRS would be inappropriate will be monitored for suicidality based on clinical impression. If the investigator is unable to conduct the C-SSRS screening, for example due to developmental disability, the reason for noncollection must be captured in the eCRF.

The C-SSRS will be administered and scored by the investigator or qualified personnel throughout the study as indicated in the Schedules of Assessments (Table 10 and Table 11).

9.4. Specific Study Period Information

A complete list of study assessments to be performed at the study center during the study periods by visit is provided in the Schedules of Assessments (Table 10 and Table 11).

Study visits during the Long-Term Treatment 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. If any study visits during the Long-Term Treatment 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, [redacted]) may be rescheduled. Any visit assessments that are missed or conducted outside the visit window will be recorded as COVID-19 related protocol deviations.

9.4.1. Screening Period [redacted]

After providing parental or legal guardian informed consent with pediatric assent from developmentally capable subjects, subjects who do not enroll directly from or participate in Study NBI-827104-CSWS2010 will be screened to determine eligibility between [redacted] that may be completed in 1 or more visits.

At least 4 days of baseline [redacted] data should be collected during the Screening Period.

During screening, parent(s)/caregiver(s) of subjects who do not enroll directly from or participate in Study NBI-827104-CSWS2010 will be instructed or retrained by site personnel on how to self-administer the [redacted] at study visits.

All screening procedures must be completed, and results must be evaluated by the investigator before the procedures are performed on Day 1. Rescreening is permitted if a subject does not meet all eligibility requirements and returns to be rescreened. A subject that has failed screening twice may not be rescreened again without prior permission from the Sponsor.

Subjects who did not participate in Study NBI-827104-CSWS2010 and who do not meet inclusion criterion #2 and #3 (Section 5.2.1) at their initial screening in Study NBI-827104-CSWS2025 will not be eligible for rescreening.

9.4.1.1. Diagnosis Confirmation Panel

For subjects who did not participate in Study NBI-827104-CSWS2010, an external DCP will review and confirm that the subject meets the clinical diagnosis of EECSWS to determine study eligibility prior to Day 1. Medical history information, as well as any further medical information supporting the diagnosis if available (including the screening [redacted]), will be provided to the DCP to review to confirm the diagnosis. A DCP charter will describe the responsibilities and data review procedures.

9.4.2. Treatment Period [redacted]

9.4.2.1. Dose Titration Period [redacted]

Subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible to be enrolled into the study on Day 1.

For subjects who enroll directly from Study NBI-827104-CSWS2010, informed consent/assent will be provided on Day 1 or within 28 days prior to Day 1 before any assessments are performed for the current study. Medical history from Study NBI-827104-CSWS2010 will be updated. Parent(s)/caregiver(s) will be instructed on how to self-administer the [redacted] on Day 1 only if they were not trained during screening in Study NBI-827104-CSWS2010.

For subjects who do not enroll directly from or participate in Study NBI-827104-CSWS2010, medical history will be updated from screening on Day 1 and [redacted] may be performed up to 4 days prior to Day 1.

Vital signs, ECG, and clinical laboratory assessments should be performed before the first dose of study treatment is administered on Day 1. The first dose of study treatment will be taken at the study site.

Subjects will begin study treatment at DL 1 based on weight group on Day 1 (Table 1). Study treatment dose may be increased to DL 2 and DL 3 during the Dose Titration Period based on investigator judgment. [redacted] the study site will call the parent(s)/caregiver(s) to assess for any AEs and determine dose titration or adjustment.

9.4.2.2. Long-Term Treatment Periods A, B, and C [redacted]

Subjects may enter Long-Term Treatment Period B after completing the [redacted] Dose Titration Period. Subjects who do not tolerate DL 3 or who are otherwise not candidates for dose escalation will continue in Long-Term Treatment Period A at their highest tolerated DL (DL 1 to 3) until the [redacted] End of Long-Term Treatment Visit or ET. Dose escalation to DL 4 (and DL 5, if applicable) and treatment during Long-Term Treatment Periods B and C will be performed as described in Section 4.1.3.

Tolerability of the subject's currently assigned DL will be assessed at each study visit. Investigator assessment of tolerability will include a review of AEs and [redacted] data as well as discussion with parent(s)/caregiver(s). Confirmation that these activities have been performed will be indicated in the eCRF.

Study Site Visits

Study assessments may be performed before or after the administration of study treatment, except on study visits in which dose is being changed ([redacted]) and [redacted]. Subjects should withhold their study treatment on days of dose changes and [redacted] until after completion of predose assessments. Additionally, vital sign measurements and ECG assessments should be performed prior to any blood sample collection.

Phone Calls

At certain timepoints in the study, phone calls with the study site will be used to perform assessments as indicated in the Schedule of Assessments (Table 10 and Table 11).

Discontinuation

Subjects receiving DL 3 or higher who discontinue study treatment at any time before the end of long-term treatment should undergo dose de-escalation if appropriate to avoid potential withdrawal seizures due to abrupt treatment discontinuation. The subject's current dose would be reduced, based on the investigator's judgment and medical urgency, in a stepwise manner over a period of up to [redacted]. Guidance for implementing a more rapid de-escalation will be provided as needed to the investigator by the Medical Monitor on an individual basis based on clinical judgment. Subjects receiving DL 1 who discontinue study treatment do not require dose de-escalation. Subjects who discontinue study treatment will be withdrawn from the study.

9.4.3. Dose Taper Period [redacted]

At the end of their final Long-Term Treatment Period (A, B, or C), subjects will begin the Dose Taper Period.

During the Dose Taper Period, the study treatment is tapered to avoid potential withdrawal seizures due to abrupt treatment discontinuation and ensure all subjects have discontinued NBI-827104 [redacted] as shown in Table 5. Subjects who are receiving DL 1 or 2 at the end of their final Long-Term Treatment Period do not need to undergo dose tapering and can immediately enter the Safety Follow-Up Period.

Table 5: Dose Taper Procedure

Dose Level at End of Long-Term Treatment Period	**Dose Level During Taper Period**		
	[redacted]	[redacted]	[redacted]
Dose Level 1 or 2	Off treatment (start Safety Follow-Up)	Not applicable (Safety Follow-Up)	
Dose Level 3	Dose Level 2	Off treatment (start Safety Follow-Up)	Not applicable (Safety Follow-Up)
Dose Level 4	Dose Level 3	Dose Level 2	Off treatment (start Safety Follow-Up)
Dose Level 5	Dose Level 4	Dose Level 3	Dose Level 2

9.4.4. Safety Follow-Up Period [redacted]

9.4.4.1. Safety Follow-Up Call [redacted]

During the Safety Follow-Up Period, approximately [redacted] after the last dose of study treatment, the study site will call the parent(s)/caregiver(s) to collect AE information.

9.4.4.2. End of Study [redacted]

The Safety Follow-Up Visit is the final study visit.

10. ADVERSE EVENTS

All AEs, whether observed by the investigator, reported by the subject, noted from laboratory findings, or identified by other means, will be recorded from the time the subject has signed the informed consent form (ICF) (for subjects who do not enroll directly from or participate in Study NBI-827104-CSWS2010) or Day 1 (for subjects who enroll directly) until the subject's final study visit (or upon ET).

10.1. Definition

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that occurs after enrollment into the study and which does not necessarily have a causal relationship with the study 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.

A treatment-emergent adverse event (TEAE) is an AE that started or worsened in severity following the first dose of study treatment.

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

- Worsening or change in nature, severity, or frequency of conditions present at the start of the study
- Subject deterioration beyond what would be expected due to the primary illness
- Intercurrent illness
- Drug interaction

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

Subjects or parent(s)/caregiver(s) 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:

- Seizures will not be considered an AE unless there is a significant increase in seizure frequency, a new seizure type, occurrence of status epilepticus, and/or in the investigator's opinion it should be captured as an AE.
- Continuous persistent disease/symptom present before study treatment administration, unless it unexpectedly progresses, or increases in severity following study treatment administration

- Study treatment failure or lack of efficacy
- Pregnancy
- Overdose of either study treatment or concomitant medication without any clinical signs or symptoms

10.1.1. Intensity of Adverse Events

Adverse events must be graded for intensity. An intensity category of mild, moderate, or severe, as defined in Table 6, 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 6: Intensity of Adverse Events

Grade	Intensity
Mild	An AE 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 AE 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 AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

AE=adverse event.

10.1.2. 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 7. An AE is deemed associated with the use of the study treatment "if there is a reasonable possibility that the treatment caused the AE" (otherwise referred to as a suspected adverse reaction). Reasonable possibility means there is evidence to suggest a causal relationship between the study treatment and the AE (Title 21 Code of Federal Regulations [CFR] 312.32 [a]).

Table 7: Relationship of Adverse Events to Study Treatment

Relationship	Description
Definite	The AE follows a reasonable temporal sequence from administration of the study treatment, abates upon discontinuation of the study treatment, follows a known or hypothesized cause-effect relationship, and (if appropriate) reappears when the study treatment is reintroduced.
Possible	The AE follows a reasonable temporal sequence from administration of the study treatment and cannot be reasonably explained by the known characteristics of the subject's clinical state, environmental, or toxic factors, or other modes of therapy administered to the subject. There should be some evidence to support a causal relationship between the study treatment and the AE.

Relationship	Description
Unlikely	The temporal sequence between the AE and the study treatment is such that the study treatment is not likely to have any reasonable association with the AE or other plausible explanations exist for the AE (eg, disease, other drugs).
Not related	The AE does not follow a reasonable temporal sequence from administration of the study treatment, may not abate upon discontinuation of the study treatment, does not follow a known or hypothesized cause-effect relationship, and (if applicable) may not reappear when the treatment is reintroduced, furthermore, there may exist a clear alternative medical explanation (eg, underlying disease state) or association with study procedure or study conduct.

AE=adverse event.

10.2. Recording Adverse Events

For enrolled 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.

10.3. Poststudy Follow-Up of Adverse Events

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

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

10.4. Serious Adverse Events

All SAEs will be recorded from the time the subject has signed the ICF (for subjects who do not enroll directly from Study NBI-827104-CSWS2010) or Day 1 (for subjects who enroll directly) until the final study visit. Investigators are not obligated to actively seek SAEs after a subject has withdrawn from or completed the study. However, if the investigator learns of any SAE, including a death, at any time after a subject has been withdrawn from or has completed the study, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor as described in Section 10.4.3.

10.4.1. Definition of a Serious Adverse Event

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

- Death.
- A life-threatening AE. Life-threatening means that the subject was, in the view of the investigator or Sponsor, at immediate risk of death from the reaction as it occurred. It does not mean that hypothetically the event might have caused death if it occurred in a more serious form.
- Inpatient hospitalization or prolongation of existing hospitalization. Hospitalization for elective treatment or a preexisting condition that did not worsen during the clinical investigation is not considered an AE. Hospitalization or nursing home admission for the purpose of caregiver respite is not considered an AE. Complications that occur during hospitalization are AEs, and if a complication prolongs hospitalization, the event is considered serious. Treatment in a hospital emergency room is not a hospitalization.
- A persistent or significant incapacity or substantial disruption of a person's ability to conduct normal life functions.
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization. These events may be considered serious when, based on appropriate medical judgment, they may jeopardize the health of the subject and may require medical or surgical intervention to prevent one of the outcomes listed. Any other event thought by the investigator to be serious should also be reported, following the reporting requirements detailed in this section. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

10.4.2. Managing Serious Adverse Events

Subjects experiencing an SAE or an emergency situation will be examined by a physician as soon as possible. The physician in attendance will do whatever is medically needed for the safety and well-being of the subject. The subject will remain under observation as long as medically indicated. Appropriate laboratory studies will be conducted until all parameters return to normal or are otherwise explained or stable. The subject will be followed until the SAE resolves or until the subject is medically stabilized.

10.4.3. Reporting Serious Adverse Events and Other Immediately Reportable Events

SAEs and pregnancies must be reported within 24 hours of first knowledge of the event by study personnel to Neurocrine Biosciences, Inc. (NBI) Drug Safety and Pharmacovigilance (DSPV). Reports of SAEs and pregnancies must be followed by a fax or email of the SAE or Pregnancy Form (Table 8). It is important that the investigator provides his or her assessment of relationship to study treatment at the time of the initial SAE report. The investigator (or designee) will also

notify the IRB/IEC, if necessary) of the SAE and the outcome of the SAE, as required by the IRB/IEC.

Additionally, the following category of medical events that could occur during participation in a clinical study must be reported within 24 hours to the study Medical Monitor: 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 or clinical impression. Contact information for the study Medical Monitor will be provided to the study sites.

Table 8: Contact Information for Drug Safety and Pharmacovigilance

Facsimile	[redacted]
Email	[redacted]

10.4.4. Expedited Safety Reports

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

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.

10.5. Urgent Safety Measures

If an event occurs that is related to the conduct of the study or the development of the study treatment, and this new event is likely to affect the safety of subjects, the Sponsor and the investigator will take appropriate urgent safety measures to protect subjects against any immediate hazard. The Sponsor will work with the investigator to ensure the IRB/IEC and local regulatory authority are notified within 3 days or in accordance with applicable local laws and regulations.

10.6. Pregnancy

Pregnancy is neither an AE nor an SAE unless the criteria for an SAE are met. However, all pregnancies in subjects who received NBI-827104 will be followed to assess for pregnancy outcome. Subjects of childbearing potential must be counseled at all visits to continue using contraception (inclusion criterion #3, Section 5.1) until 90 days after the last dose of study treatment. If a female subject believes she is pregnant at any time between signing the ICF and the last study visit, she should return to the study center within 24 hours and undergo a serum pregnancy test. Female subjects confirmed to be pregnant will be discontinued from the study treatment and withdrawn from the study.

All confirmed pregnancies in female subjects or in female partners of male subjects who received study treatment must be immediately reported to NBI (contact information is provided in Section 10.4.3), followed by fax or email of the pregnancy form to NBI DSPV. 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).

Male subjects with female partners who become pregnant during the study must notify the study center as soon as possible. The study center will ask to follow the subject's partner's pregnancy.

11. STATISTICAL METHODS

This section represents a brief description of the planned primary analysis of the primary and secondary endpoints. A comprehensive and detailed statistical analysis plan (SAP) will be generated and finalized prior to study database lock. The SAP will provide additional details regarding the methods of analysis summarized in this protocol, describe analysis methods for other endpoints, describe analyses to characterize the study conduct and population, and may describe sensitivity and supplementary analyses for selected endpoints.

11.1. Statistical Hypothesis

There will be no formal hypothesis testing of the primary endpoint.

11.2. Sample Size Determination

A total sample size of up to approximately 24 male and female subjects is based on the sample size of Study NBI-827104-CSWS2010. At least 12 subjects are targeted to complete Week 12 at the highest DL evaluated in the study.

11.3. Analysis Sets

Statistical analysis sets used in this study are defined in Table 9. Additional analysis sets may be specified in the SAP.

Table 9: Analysis Sets

Population	Description
Full analysis set	The full analysis set will include all enrolled subjects who receive at least 1 dose of study treatment and have any efficacy data collected after the Day 1 Visit.
Safety analysis set	The safety analysis set will include all enrolled subjects who take at least 1 dose of study treatment.
[redacted]	[redacted]

11.4. Endpoints

For the endpoints below, [redacted]. The Treatment Period includes a [redacted] Dose Titration Period. Additional endpoints may be described in the SAP.

11.4.1. Primary (Safety)

- The occurrence of serious TEAEs.

11.4.2. [redacted]

11.4.2.1. [redacted]

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

11.4.2.2. [redacted]

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

11.4.2.3. [redacted]

- [redacted]

11.5. Statistical Analyses

Descriptive statistical methods will be used to summarize the data from this study. Descriptive statistics typically include the number of subjects (n), mean, standard deviation or standard error, median, first and third quartile, minimum, maximum, and CIs for continuous variables; and refers to the number and percentage of subjects for categorical variables.

Unless otherwise specified, the assessments collected at the Day 1 Visit will be used as baseline. [redacted] Additional definitions of baseline may be specified in the SAP.

11.5.1. [redacted]

[redacted]

11.5.2. Safety Analyses

The subject incidence of serious TEAEs, TEAEs leading to discontinuation of study treatment, and fatal TEAEs will be summarized using descriptive statistics.

Additional summaries of TEAEs, including summaries by system organ class and preferred term, will be provided.

Descriptive statistics will be generated for additional safety data, including selected laboratory analytes, vital signs, body weight, ECG parameters, and C-SSRS, which will be further described in the SAP.

11.5.3. [redacted]

[redacted]

11.6. Interim Analyses

11.6.1. Data Monitoring Committee

An independent DMC will periodically review accumulating study data to avoid exposing subjects to excessive risk as a result of the study procedures and treatment. The DMC will consist of at least 3 members, including physicians and a statistician with expertise in the areas of clinical trials, epileptology, and biostatistics. The data review may result in recommendation for early termination of the study or changes to the protocol and informed consent. A DMC charter will describe the responsibilities, timing of meetings, and data review procedures.

11.6.2. Interim Analysis

The Sponsor will review the safety, tolerability, [redacted] of NBI-827104 DL 4 to determine if the study will continue, with the possibility to increase the maximum dose level for the study to DL 5 [redacted]

This review will guide the selection of doses for DL 5, if applicable. [redacted]

An independent DMC (Section 11.6.1) will also review the safety and tolerability data [redacted] and make a recommendation to the Sponsor for whether the study may continue per the protocol.

12. SUPPORTING DOCUMENTATION

12.1. Case Report Forms

The eCRF data for this study are being collected with an electronic data capture (EDC) system (Rave®) provided by [redacted], New York, United States (US). 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 vendor, [redacted], 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 investigator should review the eCRFs as soon as possible after the subject visit has occurred and electronically sign the eCRFs as soon as possible after the subject completes or discontinues from the study.

The investigator or an authorized member of the investigator's staff will make any necessary additions/corrections to the eCRF. All change information, including the date, person performing the corrections, and reason for the change will be available via the electronic audit trail, which is part of the EDC system. The eCRFs will be reviewed periodically for completeness, legibility, and acceptability by 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.

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

All clinical work conducted under this protocol is subject to Good Clinical Practice (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 on-line by authorized study center personnel. After data is entered into EDC, automated (computer-generated) logic checks will run in order to identify items such as inconsistent study dates. In addition, manual review/checks may be performed by 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), per the Sponsor. Prior and concomitant medications will be coded using the chosen version of the World Health Organization Drug Dictionary, per the Sponsor.

12.4. Ethics

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

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

12.5. General Legal References

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

12.6. Institutional Review Board/Independent Ethics Committee

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

A list of members participating in the IRB/IEC 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 IRB/IEC meeting, it must be clear that this person did not vote.

12.7. Protocol Adherence – Amendments

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

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

12.8. 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 protocol and ICF
- Copy of the IRB/IEC approved written ICF to be used
- Laboratory documents (certifications/accreditations, normal ranges) if not provided by a central laboratory

12.9. Informed Consent/Assent

The subject's parent(s) or legal guardian(s) will provide informed consent with signed and witnessed pediatric assent for subjects determined by the investigator to be capable of providing assent according to national laws and regulations before the performance of any study related procedures. Informed consent/assent may be done remotely, if allowed per site and remote consenting procedures are in place.

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

12.10. Study Monitoring

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

of the investigator study file to ensure completeness of documentation in all respects of clinical study conduct.

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

12.11. Quality Assurance

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

12.12. Record Retention

Study records should be retained in compliance with federal, national, and/or local 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.

12.13. Confidentiality and Data Protection

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. Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

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 with the laws and regulations of the country in which the study is conducted, the investigator is obliged to provide the Sponsor with the complete test results and all data compiled in this study.

12.14. Publication and Disclosure 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.

The Sponsor will submit study results for posting on public registry(ies) as required for compliance with applicable laws and/or regulations in the region(s) where the study is being conducted. For the purposes of study results disclosure, study completion is defined as the date of the last visit or procedure for the last subject in the study globally.

13. STUDY COMMENCEMENT AND DISCONTINUATION

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

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

14. REFERENCES

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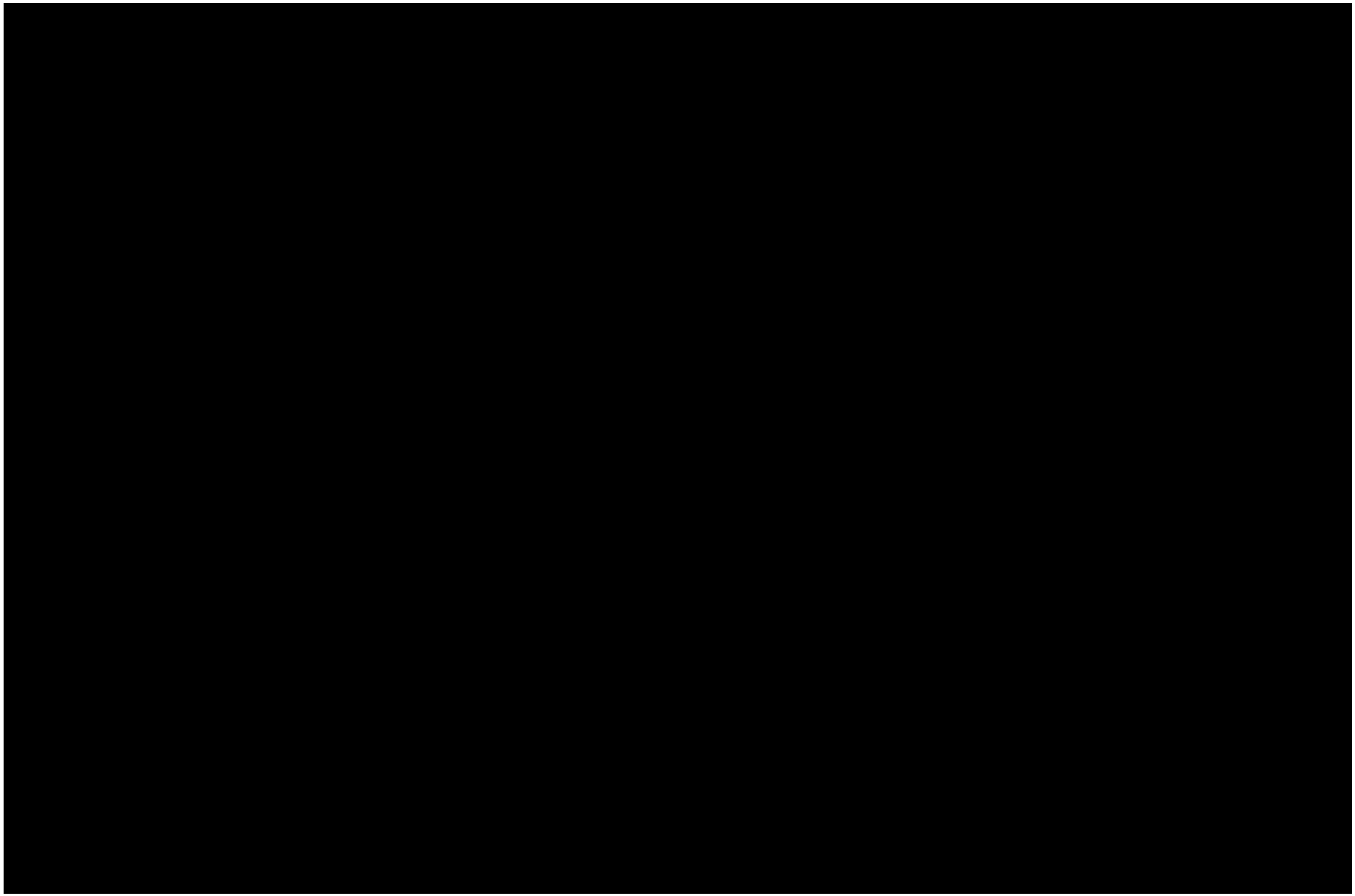
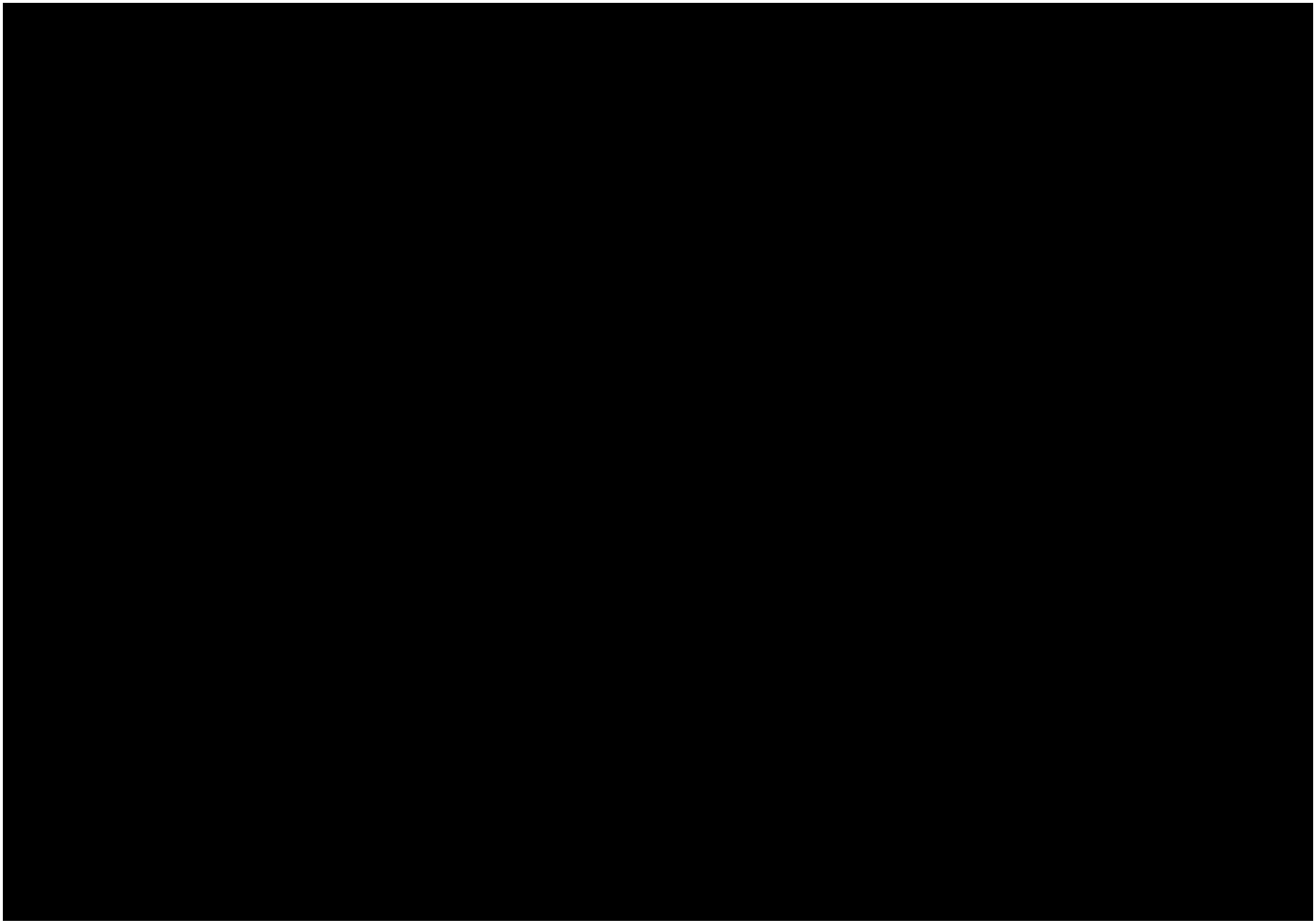
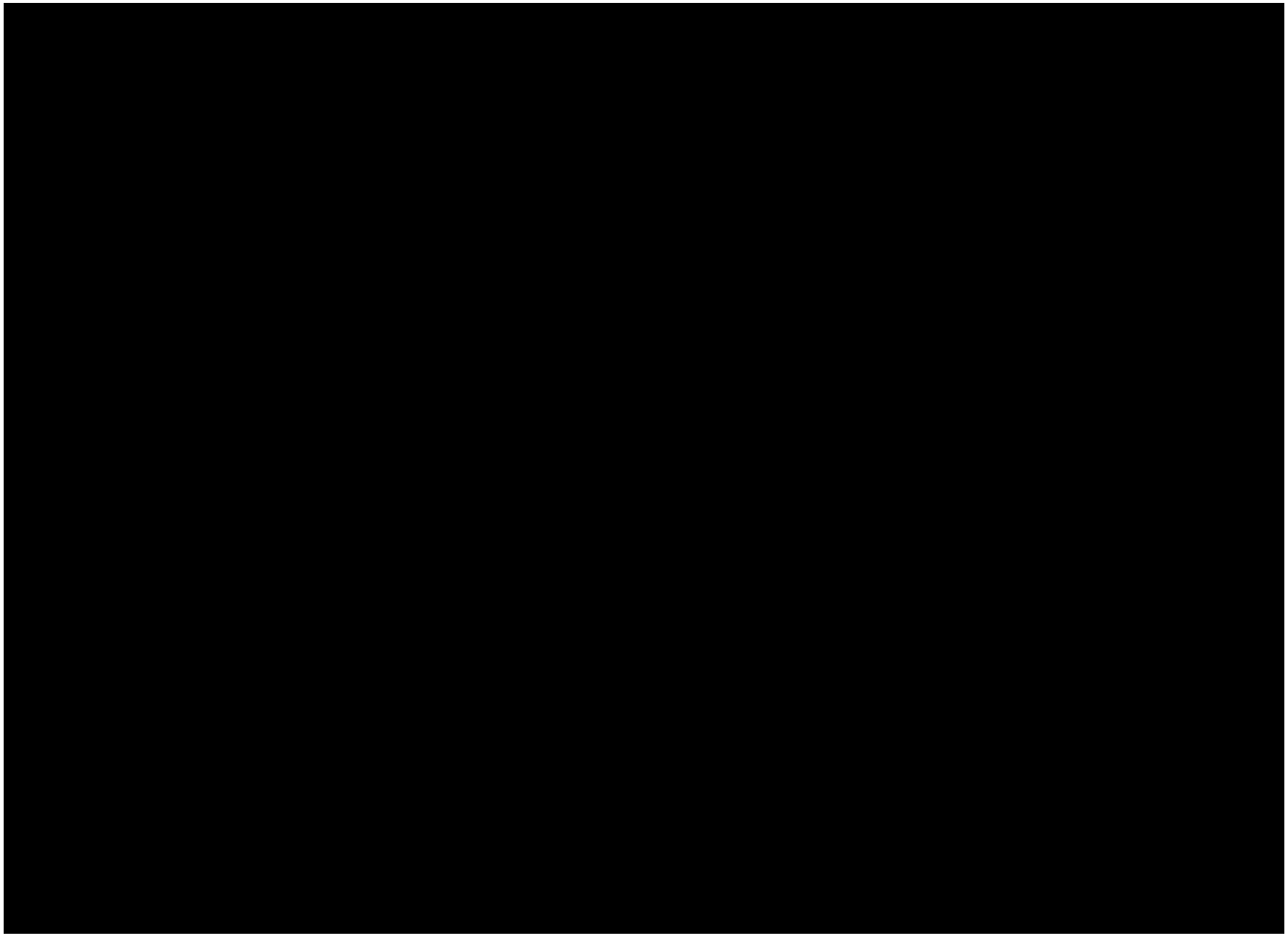
Appendix A. SCHEDULES OF ASSESSMENTS

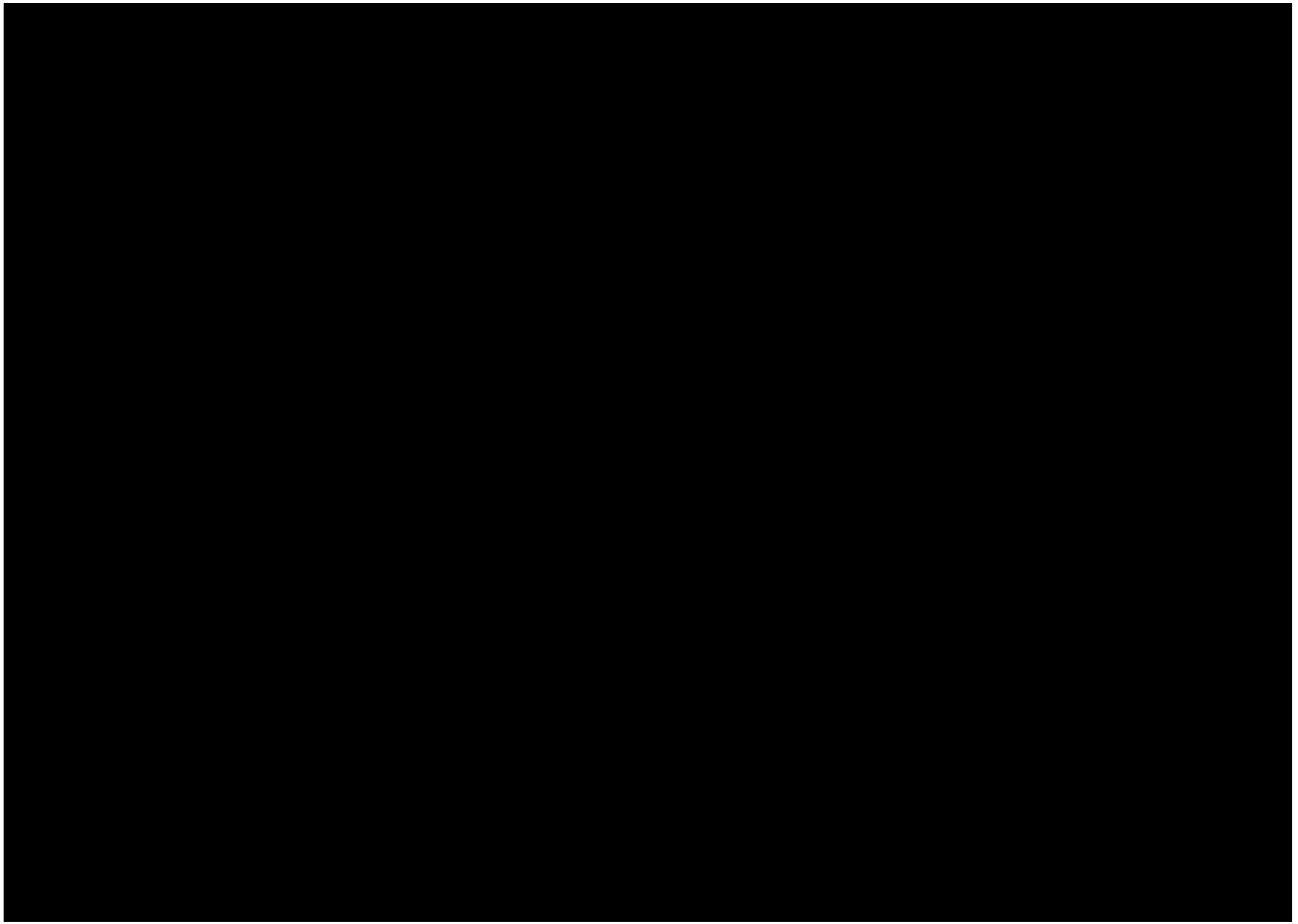
Table 10: [redacted]

[redacted]









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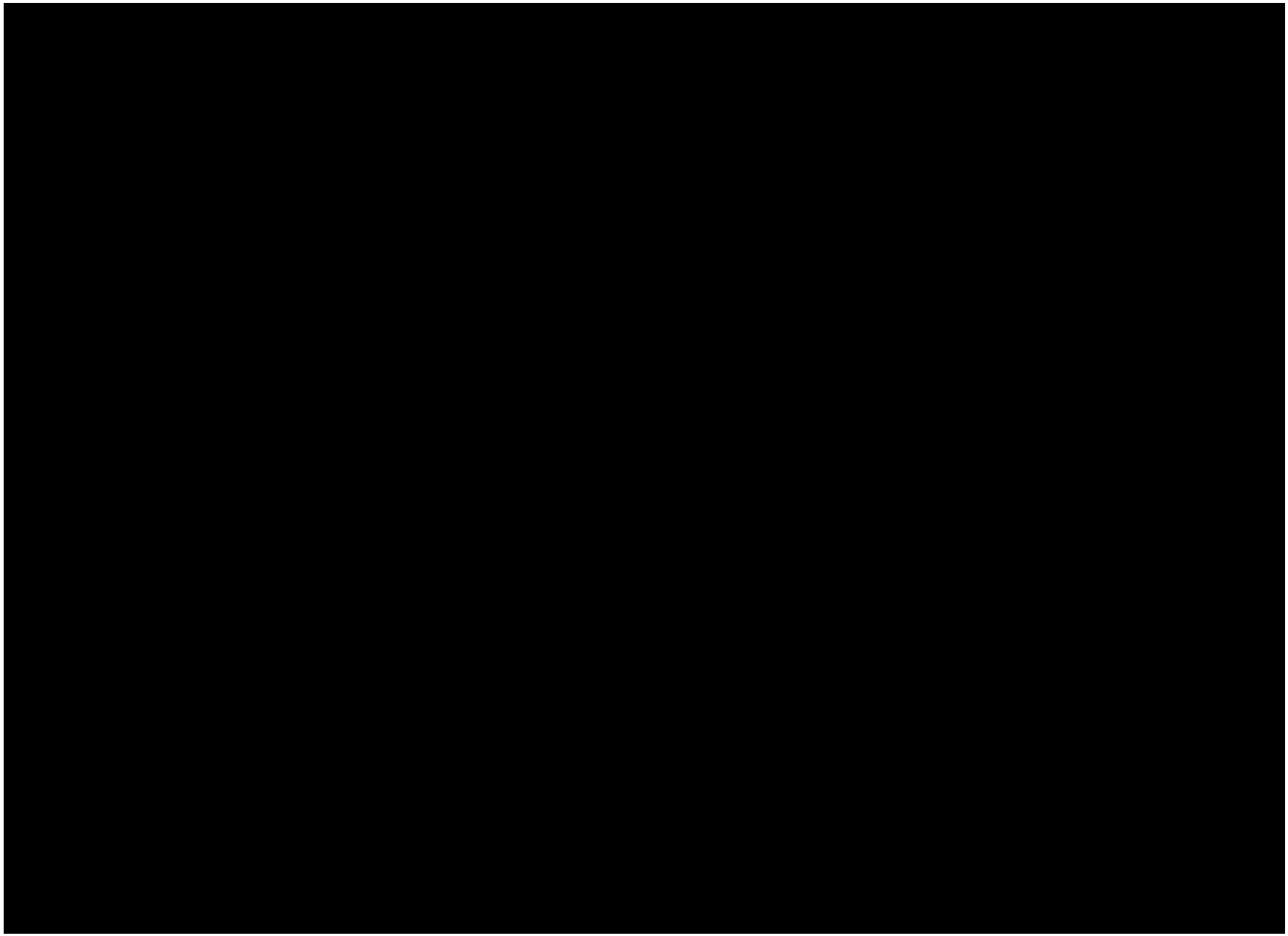

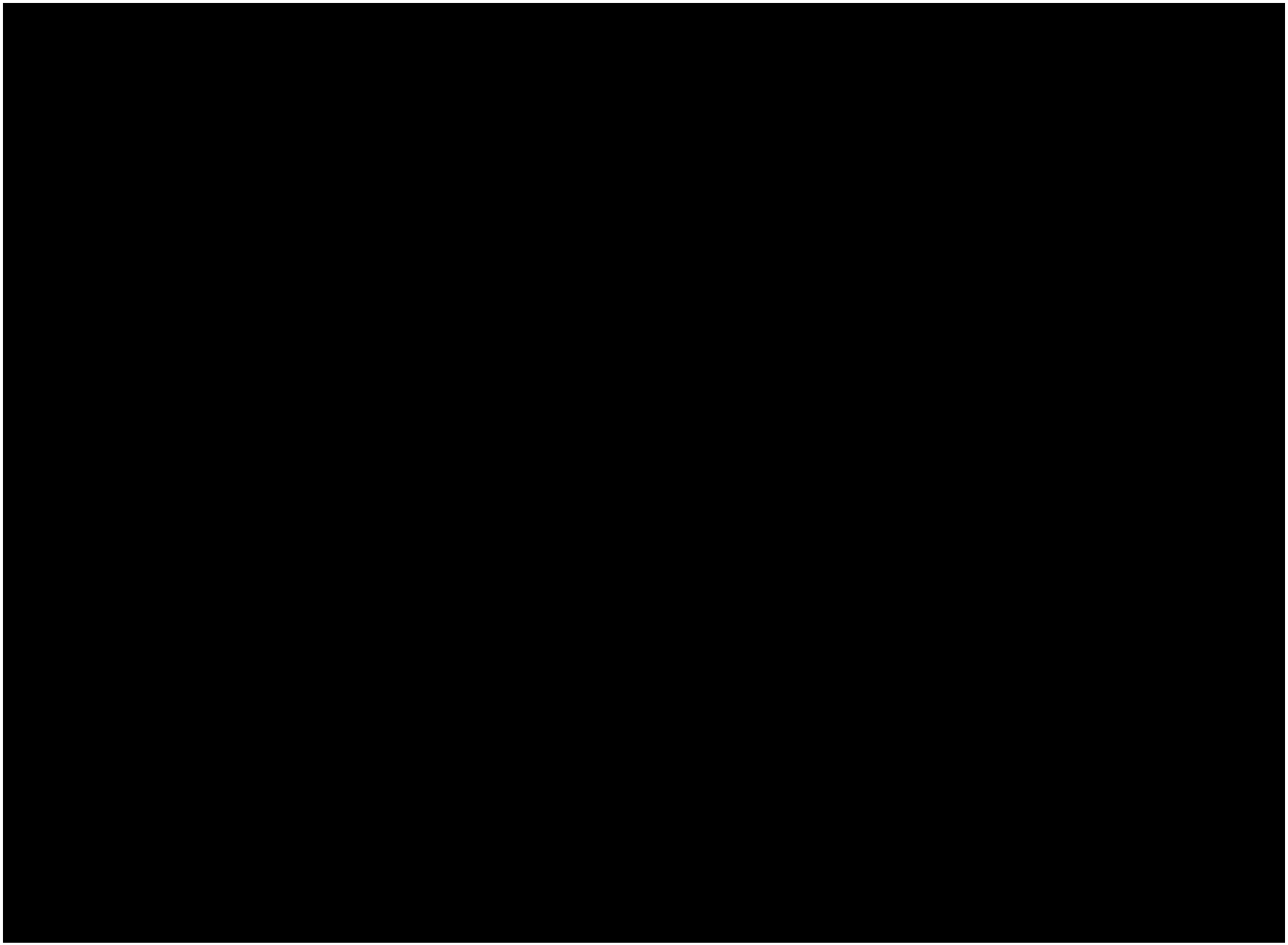

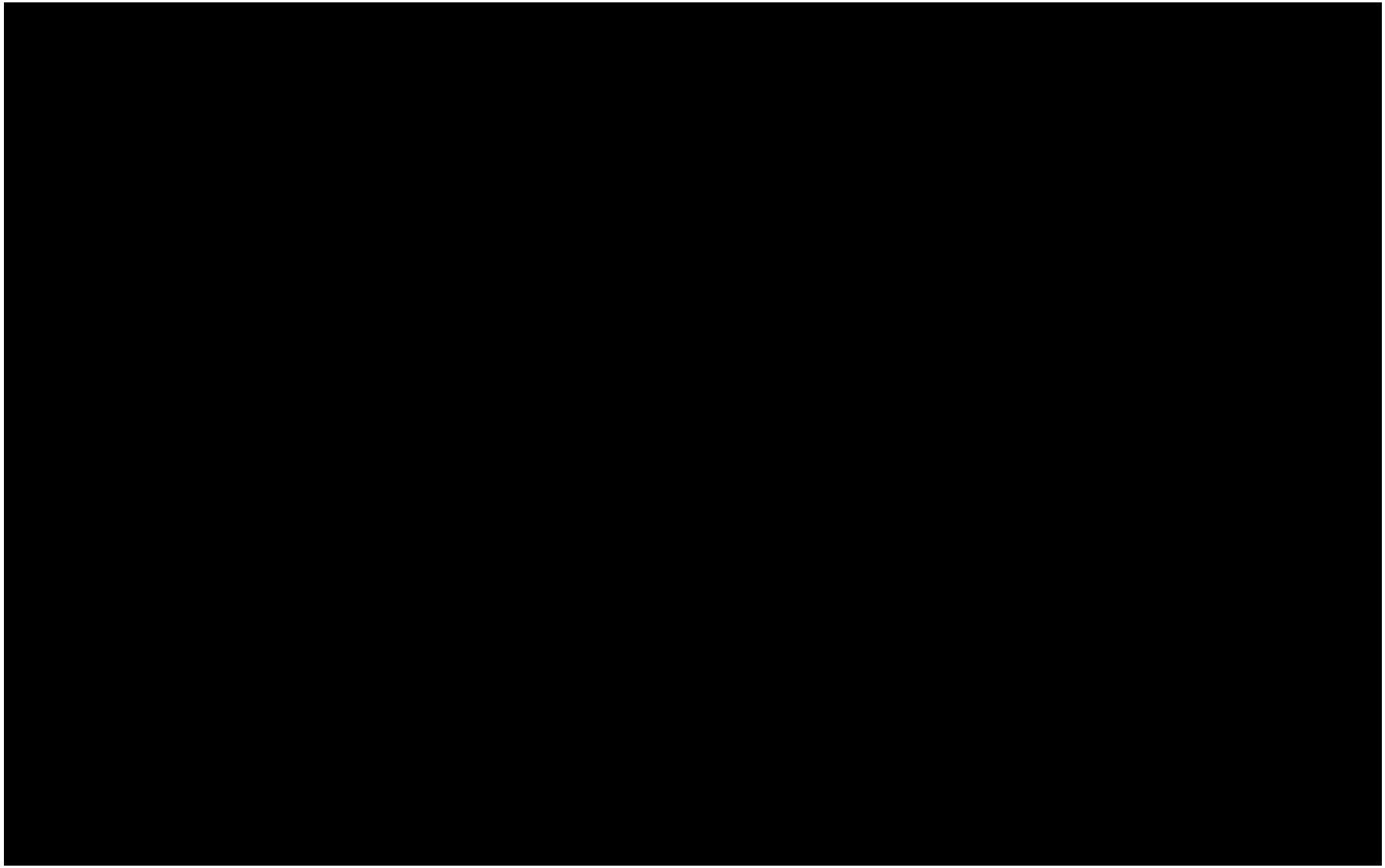

APPENDIX B. INVESTIGATOR SIGNATURE

CLINICAL STUDY TITLE: Long-Term, Open-Label Extension Study to Evaluate the Safety and Tolerability of NBI-827104 in Pediatric Subjects with Epileptic Encephalopathy with Continuous Spike-and-Wave During Sleep

PROTOCOL No.: NBI-827104-CSWS2025

As Agreed:

_____ _____

Principal Investigator Signature Date

PRINCIPAL INVESTIGATOR:

_____

(Print Principal Investigator Name)

STUDY CENTER:

_____

(Print Study Center Name)

APPENDIX C. SPONSOR APPROVAL SIGNATURE

The undersigned has reviewed and approves the content of this document.

[redacted] Electronically signed and dated

[redacted]
Neurocrine Biosciences, Inc.
[redacted]
San Diego, CA [redacted]
United States

Signature Date

Signature Page for VV-CLIN-002592 v2.0

Approval Task	[redacted] Clinical 07-Apr-2023 19:10:33 GMT+0000

Signature Page for VV-CLIN-002592 v2.0