NCT #: NCT05301894

STATISTICAL ANALYSIS PLAN
PHASE 2

Version: 1.0

Date: 6 September 2024

Based on: Protocol Amendment [redacted]

Study Treatment: NBI-827104

Study Number: NBI-827104-CSWS2025

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

Study Sponsor: Neurocrine Biosciences, Inc.

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This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

CONFIDENTIAL

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Neurocrine Biosciences, Inc.

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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ASM	Antiseizure medication
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
[redacted]	[redacted]
BLQ	Below the lower limit of quantification
BMI	Body mass index
[redacted]	[redacted]
CI	Confidence interval
[redacted]	[redacted]
[redacted]	[redacted]
CSWS	Continuous spike-and-wave during sleep
COVID-19	Coronavirus disease 2019
C-SSRS	Columbia-Suicide Severity Rating Scale
[redacted]	[redacted]
CV	Coefficient of variation
DL	Dose Level
DMC	Data Monitoring Committee
eCRF	Electronic case report form
EECSWS	Epileptic encephalopathy with continuous spike-and-wave during sleep
EEG	Electroencephalogram
EMA	European Medicines Agency
ET	Early termination
FDA	US Food and Drug Administration
GGT	Gamma-glutamyl transferase
GMR	Geometric mean ratio
ICH	International Council for Harmonization
ID	Identification
IPDs	Important protocol deviations

Abbreviation	Term
IVIG	Intravenous Immunoglobulin
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
NBI	Neurocrine Biosciences, Inc.
NREM	Nonrapid eye movement
OL	Open-Label
[redacted]	[redacted]
PT	Preferred term
REM	Rapid eye movement
QTcF	QT interval corrected for heart rate using Fridericia's correction
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical analysis system
SD	Standard deviation
SE	Standard error
SMQ	Standardized MedDRA Query
SOC	System organ class
SWI	Spike-wave index
[redacted]	[redacted]
[redacted]	[redacted]
TBIL	Total bilirubin
TEAE	Treatment-emergent adverse event
tid	3 times a day
ULN	Upper limit of normal
VNS	Vagus nerve stimulator
WHO	World Health Organization

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and data displays that will be prepared to summarize the data from Neurocrine Biosciences, Inc. (NBI) Protocol NBI-827104-CSWS2025.

This SAP was developed in accordance with International Council for Harmonization (ICH) E9 guidance. All decisions regarding the final analysis will be made prior to database lock and documented in this SAP. Changes to the planned analyses described in this SAP will be statistically justified and described in the clinical study report. Further information related to study design and methodology can be found in the study protocol.

2. STUDY OBJECTIVES

2.1. Primary

The primary objective for this study is 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).

2.2. [redacted]

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

3. STUDY DESIGN

This is a Phase 2, multicenter, open-label extension, interventional study to evaluate the long-term safety, tolerability, [redacted] of NBI-827104 in pediatric subjects with EECSWS. Eligible subjects may enroll directly following completion of the Week 12 study visit at the end of the maintenance period of Study-NBI-827104-CSWS2010 (known as CSWS2010 hereafter) or after a gap following completion of that study. Subjects who did not participate in CSWS2010 may enroll if [redacted]. This study is expected to enroll approximately 24 subjects aged 4 to 12 years (inclusive).

The study will consist of the following periods: a Screening Period [redacted], which is applicable only for subjects who do not enroll directly from or did not participate in CSWS2010; a Dose Titration Period [redacted]; a Long-Term Treatment Period [redacted]; a Dose Taper Period [redacted]; a Safety Follow-up Period [redacted]. The maximum duration of an individual subject's study participation is up to 242 weeks. For subjects who enroll directly from CSWS2010, the CSWS2025 Day 1 Visit is the same as the CSWS2010 Day 84/Week 12 (End of Maintenance) Visit. Assessments completed as part of the End of Maintenance Visit in CSWS2010 will be transferred to the CSWS2025 Day 1 electronic case report form (eCRF).

A complete Schedule of Assessments is provided in the study protocol.

Screening Period: For subjects who enroll directly from CSWS2010, informed consent/assent may be provided within 28 days prior to Day 1 or on Day 1. Subjects who do not enroll directly or did not participate in CSWS2010 must be provided with informed consent/assent before the start of screening assessments and will be screened to determine eligibility up to 28 days before the start of study treatment dosing on Day 1.

Open-Label (OL) Dose Titration Period (Dose Level 1 through Dose Level 3): 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]. Dose titration should be based on tolerability per investigator discretion but should be no faster than once every [redacted], except situations where breakthrough seizures or other safety issues are observed. Dose titration to DLs that a subject did not tolerate in CSWS2010 is permitted but not required. Tolerability is assessed at the end of each week during the Dose Titration Period. 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.

Long-Term Treatment Period (A, B, and C): Subjects will begin Long-Term Treatment Period A at the highest tolerated dose of the Dose Titration Period, with the potential for up to 2 additional, sequential dose escalations in Long-Term Treatment Periods B and C, as follows:

- Long-Term Treatment Period A [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 at their highest tolerated DL (DL 1 to 3) until the [redacted] End of Long-Term Treatment Visit or early termination (ET).
- Long-Term Treatment Period B [redacted]: Subjects who tolerate DL 3 for at least [redacted] in Long-Term Treatment Period A will increase their dose to DL 4 and initiate Long-Term Treatment Period B. [redacted]. If the data support an increase to DL 5, the maximum DL for the study will be increased to DL 5 [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.
- Long-Term Treatment Period C [redacted], if applicable: If the evaluation of safety, tolerability, and [redacted] of at least [redacted] who escalate to DL 4 support increasing the maximum dose level of the study to DL 5, subjects who tolerate DL 4 for at least [redacted] in Long-Term Treatment Period B will increase their dose to DL 5 and initiate Long-Term Treatment Period C. Subjects will continue in Long-Term Treatment Period C at their highest tolerated DL (DL1 to 5) until the [redacted] End of Long-Term Treatment Visit of 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 [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 study, subjects may change weight groups. Subjects will begin each DL based on their body weight category as shown in the table below; 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 their new weight group.

Table 1: [redacted]

[redacted]

Initiation or adjustments of concomitant antiseizure medications (ASMs), vagus nerve stimulator (VNS) settings, and/or a ketogenic diet are not allowed for [redacted] prior to Day 1 and through the first [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 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.

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

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 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 [redacted]. 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.

3.1. Randomization

There is no randomization as this is a single-arm, OL study. Subjects will receive NBI-827104 doses according to their body weight category outlined in Table 1.

3.2. Data Monitoring Committee (DMC)

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.

The independent DMC will also review the safety and tolerability data from at least [redacted] and make a recommendation to the Sponsor for whether the study may continue per the protocol.

A DMC charter describes the responsibilities, timing of meetings, and data review procedures. DMC reports will be provided by an independent statistical center.

3.3. Blinding

There is no blinding for this study.

3.4. Sample Size Considerations

A total sample size of up to approximately 24 subjects is based on the sample size of CSWS2010. [redacted]

4. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

4.1. General Statistical Procedures

All analyses described in this plan are considered a priori analyses in that they have been defined prior to locking the study database. Analyses defined subsequent to locking the database will be considered post hoc analyses and will be applied as exploratory methodology. Any post hoc analyses will be statistically justified and described in the clinical study report. Statistical analysis will be conducted, and all tables, figures, and listings generated using SAS® software (version 9.4 or later), unless stated otherwise.

Descriptive statistical methods will be used to evaluate and summarize the data from this study. The term "descriptive statistics" refers to the number of subjects (n), mean, median, standard deviation (SD), minimum, and maximum for continuous variables. Number and percentage of subjects will be summarized for categorical variables. Descriptive analyses and summaries will be presented by all subjects, unless otherwise noted.

Summary statistics will be presented using the following decimal precision (ie, number of digits to the right of the decimal point): the minimum and maximum will have the same number of decimal places as the data; the mean, median, SD and standard error (SE) will have one more decimal place than the data being summarized; the sample size (N) will be reported as an integer; and percentages will be reported to one decimal place (percentages for zero counts are omitted and 100% will be reported as an integer). These rules may be modified if warranted, based on practical considerations.

All available study data will be included in relevant data displays, including data for subjects with incomplete or missing values. Replacement of missing data values with imputed values will generally not be performed unless specified otherwise in relevant endpoint subsections.

4.2. Analysis Sets

The following analysis sets are defined for this study in Table 2.

Table 2: Analysis Sets

Analysis Sets	Description
Full Analysis Set	The full analysis set will include all enrolled subjects who take at least 1 dose of NBI-827104 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 NBI-827104.
[redacted]	[redacted]

Summaries of subject disposition, analysis set inclusion/exclusion status, important protocol deviations (IPDs), and demographics/baseline characteristics will be based on all enrolled subjects. [redacted]-

[redacted] Efficacy analyses will be based on the full analysis set. All other summaries will be based on the safety analysis set unless otherwise noted.

4.3. General Definitions

4.3.1. Baseline Definition

Baseline [redacted]

The assessments performed at the Day 1 nominal visit of CSWS2025 will serve as the baseline value for all assessments unless otherwise noted. If a Day 1 nominal visit value is not available, then the last measurement collected prior to the first dose of NBI-827104 in CSWS2025 (hereafter known as the first dose) will serve as baseline. The Day 1 nominal visit data for direct enrollment subjects are collected during the last nominal visit (ie, [redacted]) of CSWS2010 and transferred to the Day 1 nominal visit of CSWS2025.

[redacted]

4.3.2. Derived and Transformed Data

Change from baseline is calculated as the postbaseline value minus the baseline value unless otherwise noted. Percent change from baseline is calculated as change from baseline/baseline value × 100 unless otherwise noted. If either the baseline or postbaseline value is missing, the change from baseline and/or percent change from baseline will also be missing. The percent change from baseline will also be missing if the baseline value is equal to zero.

4.3.3. Study Day

Study day is calculated relative to the date of Day 1, where Day 1 is defined as the date the subject received their first dose in CSWS2025. If the date of interest occurs on or after Day 1, then the study day will be calculated as: date of interest – date of Day 1 + 1. If the date of interest occurs prior to Day 1, then the study day will be calculated as: date of interest – date of Day 1.

4.3.4. Early Termination Data

Early termination (ET) data collected at postbaseline unscheduled visits will be mapped to the next subsequent visit where the applicable assessment would have been performed for the purpose of statistical summarization. ET data collected at a scheduled visit per the protocol schedule of assessments will be mapped to that scheduled visit for applicable data summaries.

4.3.5. Handling of Missing Data

4.3.5.1. Start Dates for Adverse Events (AEs)

Missing and incomplete dates for AEs will be imputed for the purpose of estimating the time of the event in relationship to study treatment.

The imputation rules for AE start dates are as follows:

- If the date is completely missing, the date will be imputed as the date of the first dose;
- If only the day is missing, the date will be imputed as the date of the first dose if the month and year of the AE start date match the month and year of the first dose; otherwise, the missing day will be imputed as the first day of the month;
- If both the day and month are missing, the date will be imputed as the date of the first dose if the AE start date is in the same year as the first dose; otherwise, the missing day and month will be imputed as 01 January;
- If any of the above imputations result in a start date that is later than an existing (not imputed) end date for the event, the start date will be imputed as the end date.

There will be no imputation for AE stop dates.

4.3.5.2. Start and Stop Dates for Medications

Missing and incomplete dates for medications will be imputed for the purpose of estimating the time of medication usage relative to study treatment. Medications from the antiseizure medication history eCRF page are assumed to be prior medications and imputation of dates will not be performed.

The imputation rules for medication start dates are as follows:

- If the date is completely missing, the date will be imputed as the date of the subject's first dose;
- If only the day is missing, the date will be imputed as the date of the first dose if the medication start date is in the same month and year as the first dose; otherwise, the missing day will be imputed as the first day of the month;
- If both the day and month are missing, the date will be imputed as the date of the first dose if the medication start date is in the same year as the first dose; otherwise, the missing day and month will be imputed as 01 January;
- If any of the above imputations result in a start date which is later than an existing (not imputed) medication stop date, the start date will be imputed as the stop date.

The imputation rules for medication stop dates are as follows:

- If the date is completely missing, the date will be imputed as the date of the subject's last dose;
- If only the day is missing, the date will be imputed as the date of the last dose if the medication stop date is in the same month and year as the last dose; otherwise, the missing day will be imputed as the last day of the month;

- If both the day and month are missing, the date will be imputed as the date of the last dose if the medication stop date is in the same year as the last dose; otherwise, the missing day and month will be imputed as 31 December;
- If any of the above imputations result in a stop date which is earlier than an existing (not imputed) medication start date, the stop date will be imputed as the start date.

4.4. Coding Dictionaries

Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 26.0). Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (March 2020 B3 Global version).

5. STUDY POPULATION

5.1. Disposition

The summary of subject enrollment and disposition will include:

- The total number of subjects who provided informed consent
- The following categories will be presented. The number of subjects enrolled will serve as the denominator to calculate percentages.
  - Enrolled subjects
    - Direct enrollment by CSWS2010 treatment assignment: subjects who directly rolled over from CSWS2010
    - Non-direct enrollment by CSWS2010 treatment assignment: subjects who enrolled after a gap following completion of CSWS2010
    - De novo enrollment: subjects who did not participate in CSWS2010
  - Completed study drug dosing
  - Discontinued study drug dosing, including reasons
  - Completed study
    - Last Long-Term Treatment Period completed: Schedule A
    - Last Long-Term Treatment Period completed: Schedule B
    - Last Long-Term Treatment Period completed: Schedule C
  - Discontinued study, including reasons
    - Discontinued in Schedule A
    - Discontinued in Schedule B
    - Discontinued in Schedule C

A listing will be provided which includes subject identification (ID), the date of informed consent, the date of enrollment, CSWS2010 treatment assignment, and the dose at Day 1 of CSWS2025.

5.2. Summary of Analysis Sets

A summary of the number and percentage of subjects included in (and excluded from, as applicable) each analysis set will be provided.

5.3. Protocol Deviations

Protocol deviations will be reviewed and tracked as described in the study-specific Protocol Deviation Plan. Prior to database lock, all major protocol deviations will be exported to a file and integrated into the study data.

Prior to database lock, the study team will review a listing of all major protocol deviations and determine which deviations are IPDs. IPDs are protocol deviations that might significantly affect the completeness, accuracy and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being.

A summary of the number and percentage of all enrolled subjects with IPDs by deviation category will be presented. The summary will be repeated for the subset of IPDs that are related to the coronavirus disease 2019 (COVID-19) pandemic (if applicable).

All major protocol deviations will be presented in a data listing and any that are classified as IPDs will be flagged in the listing. Any major protocol deviations related to the COVID-19 pandemic (if applicable) will also be flagged in the listing.

5.4. Demographic and Baseline Characteristics

Demographics and study baseline characteristics will be summarized descriptively for all enrolled subjects. Baseline is defined according to Section 4.3.1.

The following variables will be summarized:

- Demographics: age, age groups [redacted], sex, ethnicity, race, country
- Baseline subject characteristics: height [cm], weight [kg], body mass index [BMI, kg/m^2], Tanner stage [stage 1, 2, 3, 4, or 5]
- Baseline [redacted]
- Baseline [redacted]
- Medications: number of concomitant ASMs at baseline, number of prior ASMs, rescue medications at baseline [yes/no], non-drug antiseizure treatments at baseline [yes/no]

5.5. Medical History

Medical history information was entered into the CSWS2025 database by site staff. For subjects that participated in CSWS2010, this included the subject's medical history reported in CSWS2010 as well as any AEs from that study that were ongoing at the time of enrollment into CSWS2025. Medical history will be summarized descriptively for all enrolled subjects. Medical history data will be coded using MedDRA. Data will be summarized with frequencies and percentages of subjects with at least one medical history item, and subject frequencies and percentages according to the system organ class (SOC) and preferred term (PT) levels. The table will be sorted alphabetically by SOC and then, within an SOC, by PT.

6. IMPACT OF COVID-19 PANDEMIC

This section describes analyses and summaries that will be produced to help determine the potential impact of the COVID-19 pandemic on the study conduct/data and additional details regarding how data that is potentially impacted by the COVID-19 pandemic will be handled in the analysis plan. It is in alignment with the guidance put forth by the US Food and Drug Administration (FDA; Considerations for the Conduct of Clinical Trials of Medical Products During Major Disruptions Due to Disasters and Public Health Emergencies [March 2020, updated September 2023]) and European Medicines Agency (EMA; Points to consider on implications of Coronavirus disease [COVID-19] on methodological aspects of ongoing clinical trials [March 2020]).

To help understand the impact of the COVID-19 pandemic on the clinical trial data, the following listings will be generated:

- A listing of all subjects affected by the COVID-19 pandemic. The listing will identify subjects who experience at least one of the following situations due to the COVID-19 pandemic (additional situations may be included):
  - Discontinued study due to COVID-19
  - Presumed or confirmed diagnosis of COVID-19
  - Had at least one COVID-19 pandemic-related major protocol deviation
  - Missed at least one study visit due to COVID-19
  - Missed at least one assessment due to COVID-19
  - Required at least one assessment to be collected using a method other than what is defined in the protocol (eg, remotely) due to COVID-19
- A listing of subjects who withdrew from study due to the COVID-19 pandemic, which will include the specific reasons.
- A listing by subject of visits and assessments affected by the COVID-19 pandemic (eg, missing, partial, collected remotely).

The above listings may be omitted if it is known there was no impact of the COVID-19 pandemic on the study conduct.

The broad Standardized MedDRA Query (SMQ) of COVID-19 will be utilized to identify PTs pertaining to subjects with a presumed or confirmed diagnosis of COVID-19 (using MedDRA version 26.0).

Further classification and summaries of major protocol deviations related to the COVID-19 pandemic are detailed in Section 5.3.

7. EFFICACY

The efficacy endpoint and planned analysis methods are described below. Efficacy analyses will be based on the full analysis set. [redacted]

[redacted]

7.1. [redacted]

[redacted]

[redacted]

[redacted]

8. [redacted]

8.1. [redacted]

[redacted]

8.2. [redacted]

[redacted]

9. SAFETY

The safety objective of the study is to characterize the safety profile of NBI-827104 as measured by treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs), clinical laboratory tests, body weight, neurological and [redacted] examinations, vital signs, electrocardiogram (ECG), Columbia-Suicide Severity Rating Scale (C-SSRS), Tanner Stage, and medications. All outputs for safety endpoints will be based on the safety analysis set. The analysis of the safety data will be based on descriptive statistics and presented according to the nominal study visit unless otherwise noted. Safety data will not be subject to any imputation and will be summarized on an observed case basis. No formal hypothesis-testing analysis of safety data will be performed.

9.1. Study Drug Dosing and Compliance

The duration of exposure to study drug will be calculated as: last dose date – first dose date +1. Duration of exposure will be summarized with descriptive statistics by dose and for all subjects.

A summary of dose received will be presented by visit.

The site will enter into the eCRF whether the subject's dosing compliance since the previous visit was <50%, 50%-<80%, 80%-<90%, 90%-100%, >100%-120%, >120%, or Not Done. The number and percentage of subjects who have a dosing compliance of <80%, 80%-120%, >120%, and Not Done will be presented for each postbaseline visit.

A listing of the lot numbers will be summarized for all enrolled subjects.

9.2. Adverse Events

A TEAE is an AE not present prior to the initiation of study drug dosing in CSWS2025, or is an already present condition that worsens either in intensity or frequency following the initiation of study drug dosing in CSWS2025. It is defined by an onset date and time on or after the date of the first dose and within the 14 days after the date of the last dose. If the AE onset date and time are unknown, it will be assumed that the AE is a TEAE. If the AE onset time is unknown but the AE onset date is the same date as the first dose of study drug, it will be assumed that the AE is a TEAE. See details for imputing missing/partial start dates (Section 4.3.5.1). There will be no imputation for AE stop dates.

TEAEs, categorized by MedDRA SOC and/or PT, will be summarized in frequency tables. The frequency tables will include the number and percentage of unique subjects experiencing each event at least once during the study.

An overall summary table will be provided which summarizes the number and percentage of unique subjects with any TEAE, treatment-emergent SAE, TEAE leading to study drug dose reduction but not study drug discontinuation, TEAE leading to study drug interruption but not study drug discontinuation, TEAE leading to study drug discontinuation, TEAE leading to study discontinuation, and TEAE resulting in death. The summary table will also include the frequency distribution of the maximum TEAE intensity (mild, moderate, severe) reported for each subject.

The following summary tabulations will also be presented. Unless otherwise noted, the tables will be sorted in alphabetical order. The first line of the table will display the number and percentage of subjects with at least one of the following TEAE categories:

- TEAEs, classified by SOC and PT
- TEAEs, classified by PT, displayed in a descending order by frequency
- Treatment-emergent SAEs by SOC and PT
- TEAEs leading to study drug dose reduction, not leading to discontinuation by SOC and PT
- TEAEs leading to study drug interruptions, not leading to discontinuation by SOC and PT
- TEAEs leading to study drug discontinuation by SOC and PT
- TEAEs leading to study discontinuation by SOC and PT
- TEAEs leading to death by SOC and PT

A listing of TEAEs resulting in study drug discontinuation will be provided which includes subject ID, the dose being received at the onset time of the TEAEs leading to study drug discontinuation, study day of the discontinuation, and other relevant information from the AE eCRF.

Separate listings of SAEs, fatal AEs, and TEAEs resulting in study drug dose reductions will also be provided. In the event that no subjects experience SAEs, fatal AEs, or TEAEs resulting in study drug dose reductions, the blank listing shell will be presented with text printed in the center of the listing describing that no adverse events of that type occurred during this study.

9.3. Clinical Laboratory Data

Due to the multiple different reference ranges applied to laboratory data in this study, the hematology and clinical chemistry data will be summarized categorically by visit, rather than via observed and changes from baseline values. Categories of normal, low, and high will be derived by comparing observed values against the appropriate reference ranges provided by the central clinical laboratory.

Shift tables will be presented to display shifts from baseline to the value at each postbaseline visit during Long-Term Treatment Period A/B/C. The shift table will have five rows reflecting the shift category from baseline to each postbaseline visit. Shift categories will be as follows: normal to high, normal to low, low to high, high to low, and non-adverse shifts (ie, low to low, normal to normal, high to high, low to normal, and high to normal). A “Total” row will also be included. Subjects with a missing baseline value or who do not have postbaseline data will not be included in the tables for that variable. The number and percentage of subjects in each shift category will be displayed in the table; percentages will be based on the number of subjects included in the table.

In addition, participants who had potentially clinically significant (PCS) laboratory results will be summarized in frequency tables (ie, number and percentage) for the following clinical laboratory variables:

- [redacted]

A PCS laboratory listing will be provided which includes subject ID, age, sex, laboratory test, the dose being received prior to the assessment date, visit, date/time of collection, result, normal range, and criteria met.

9.4. Neurological, [redacted] Examinations

Frequency tables (ie, number and percentage of subjects) will be presented categorically by visit for neurological examinations including consciousness, mental status, muscle strength and tone, coordination, and gait; as well as for [redacted]

9.5. Tanner Stage

The number and percentage of subjects in each Tanner Stage will be summarized by visit. The descriptive summaries will be repeated according to sex (ie, female vs male) and age groups at Day 1 [redacted]

9.6. Vital Signs, Weight and BMI

The vital signs data, including weight, BMI, blood pressure, body temperature, and heart rate (including orthostatic values, calculated as standing value minus supine value), will be summarized with descriptive statistics by visit. Observed and change from baseline values will be presented.

9.7. Electrocardiogram

The triplicate ECG parameter values recorded at each timepoint for heart rate, PR interval, QRS duration, QT interval, and QTcF (corrected QT interval using Fridericia's formula) interval will be averaged (and rounded to the nearest whole number) for each subject and timepoint for the purpose of statistical summarization. Additionally, for the triplicate investigator overall categorical assessment (ie, Normal, Abnormal not Clinically Significant, or Abnormal Clinically Significant) at each timepoint, the outcome representing the greatest degree of abnormality will be selected for summarization.

Descriptive statistics for the observed values and change from baseline will be presented for each of the ECG parameters by timepoint.

Frequency tables (number and percentage of subjects) will be presented for the overall categorical assessment at each timepoint.

Two additional categorical summaries (frequency tables displaying number and percentage of subjects) will be presented for the QTcF interval. For the first summary, the observed QTcF values at each timepoint will be classified as follows:

- Greater than 450 msec
- Greater than 480 msec
- Greater than 500 msec

For the second categorical summary, the change from baseline to each subsequent timepoint will be classified as follows:

- Increase greater than 30 msec
- Increase greater than 60 msec

The same categorical summaries will be presented in frequency tables for values at any postdose timepoint (including unscheduled assessments) meeting the aforementioned criteria.

9.8. Columbia-Suicide Severity Rating Scale

The C-SSRS is a measure of suicidal ideation and behavior. The C-SSRS data will be presented in the following summaries:

- Screening/lifetime assessment: data will be summarized for subjects who did not enroll directly from CSWS2010.
- Baseline assessment
- Postbaseline assessments

Each summary will display the number and percentage of subjects who report "Yes" to specific C-SSRS items or categories of items (a category is assigned a "Yes" value if a "Yes" is reported for any item in the category). These C-SSRS items and categories are as follows:

- Suicidal Ideation Items

(1) Wish to be dead
(2) Non-specific active suicidal thoughts
(3) Active suicidal ideation with any methods (not plan) without intent to act
(4) Active suicidal ideation with some intent to act, without specific plan
(5) Active suicidal ideation with specific plan and intent

- Suicidal Ideation Category: Any of items (1) through (5)
- Suicidal Behavior Items

(6) Preparatory acts or behavior
(7) Aborted attempt
(8) Interrupted attempt
(9) Non-fatal suicide attempt
(10) Completed suicide ("Since Last Visit" assessments only)

- Suicidal Behavior Category: Any of items (6) through (10)
- Suicidal Ideation or Behavior Category: Any of items (1) through (10)

For the "all postbaseline assessments" summary, each subject's C-SSRS responses for all postbaseline assessments will be evaluated, and a "Yes" response for any assessment will be considered as a "Yes" for the subject.

In addition to the summaries described above, shift tables comparing postbaseline suicidal ideation scores to baseline scores will be presented. The shift table scores are defined as the following:

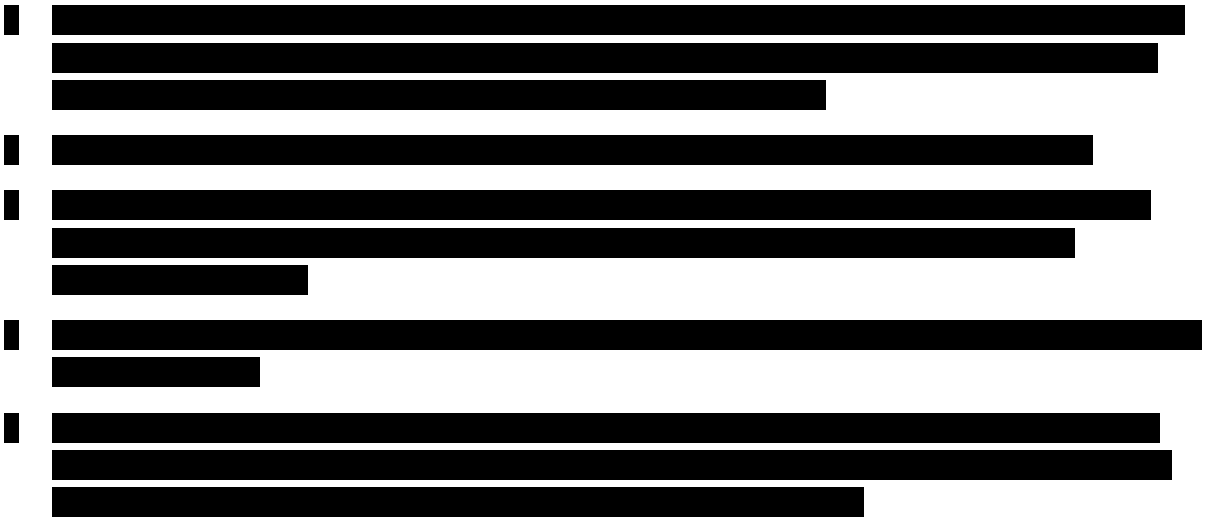
0 = No suicidal ideation
1 = Wish to be dead
2 = Non-specific active suicidal thoughts
3 = Active suicidal ideation with any methods (not plan) without intent to act
4 = Active suicidal ideation with some intent to act, without specific plan
5 = Active suicidal ideation with specific plan and intent

The shift tables will display the number and percentage of subjects within each cell of a 6 x 6 table, with the rows representing the baseline score and the columns representing the maximum score recorded across all postbaseline assessments (including both scheduled and unscheduled visits). Subjects missing either a baseline score or all postbaseline scores will not appear in the table.

9.9. Prior and Concomitant Medications

Prior and concomitant medications will be summarized by WHO Drug Anatomical Therapeutic Chemical Classification (ATC) Level 3 category (or Level 2 if there is not an applicable Level 3 category) and preferred names. Medications from the antiseizure medication history eCRF page are assumed to be prior medications and imputation of dates will not be performed. Missing start and stop dates will be handled according to Section 4.3.5.2.

Medications will be summarized in frequency tables. The frequency tables will include the number and percentage of unique subjects reporting the medication one or more times. For medications, the table will be sorted alphabetically by ATC class and then, within an ATC class, by preferred names. Prior and concomitant medications are defined as mutually exclusive categories according to the first dose as follows:



10. PERFORMANCE QUALIFICATION OF SAS® PROGRAMS

The analysis and summary of data from this study will be performed using SAS® 9.4 (or a later release if available). All SAS® programs used in the production of statistical analyses, tables, listings, and figures described in this SAP will undergo performance qualification (verification that the program produces the intended output) in accordance with department standard operating procedures. The performance qualification may include independent programming and/or peer review of the SAS® log files. In addition, tables, figures, listings, and statistical analysis output will be independently reviewed for completeness and accuracy.

11. DEVIATIONS FROM PROTOCOL PLANNED ANALYSIS

[redacted]

12. REFERENCES

European Medicines Agency. Points to consider on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials – Scientific guideline. March 2020. https://www.ema.europa.eu/en/documents/scientific-guideline/points-consider-implications-coronavirus-disease-covid-19-methodological-aspects-ongoing-clinical_en-0.pdf. Accessed July 19, 2023.

FDA. Considerations for the Conduct of Clinical Trials of Medical Products During Major Disruptions Due to Disasters and Public Health Emergencies. US Department of Health and Human Services, Food and Drug Administration. https://www.fda.gov/media/172258/download. Published Mar 2020; updated Sep 2023. Accessed June 07, 2024.

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