STATISTICAL ANALYSIS PLAN
PHASE 2

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Study Treatment: NBI-921352

Study Number: NBI-921352-DEE2012

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

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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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse event
AUC	Area under the plasma concentration versus time curve
AUC_{τ}	AUC during the dosing interval at steady state (τ = 8 hours)
C_{max}	Maximum plasma concentration
DMC	Data Monitoring Committee
ET	Early termination
ICH	International Council for Harmonization
IPDs	Important protocol deviations
MedDRA	Medical Dictionary for Regulatory Activities
NBI	Neurocrine Biosciences, Inc.
PK	Pharmacokinetics
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SEM	Standard error of the mean
SOC	System organ class
TEAE	Treatment-emergent adverse event
tid	3 times a day
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-921352-DEE2012.

Study enrollment was paused after a pre-specified interim review of safety, tolerability and pharmacokinetic (PK) data collected from a Sentinel Cohort [redacted] Enrollment was not re-opened, and the study was later terminated by the Sponsor. Therefore, this SAP includes the planned analyses and data displays related to safety, tolerability, and PK data from the Sentinel Cohort only. Analyses mentioned in the protocol for the Main Cohort are not included as this cohort was not enrolled.

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 treatment unblinding 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 AND ENDPOINTS

The objectives for this study are:

Primary

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

Secondary

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

Exploratory

- [redacted]

3. STUDY DESIGN

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

This study will include 2 separate cohorts:

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

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

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

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

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

Baseline daily seizure diary data must be collected for at least [redacted], during which the parent/caregiver will complete the daily diary to record the number and type of countable motor seizures, as well as the occurrence of noncountable seizures for recording of seizure-free days. After completion of the baseline period, final eligibility will be confirmed by the investigator after review of the baseline diary data.

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

Table 1: Titration Period Doses by Weight Group

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

tid = 3 times a day.

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

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

Subjects in both cohorts who complete the titration period will enter the [redacted] maintenance period. During the maintenance period, subjects will continue to receive their final tolerated dose from the titration period. Dose levels should not be changed during the maintenance period without prior Sponsor approval. Rescue medication is permitted at any time during the study and will not be a reason for discontinuation from study treatment. Following completion of the maintenance period, subjects will have the option to continue in the active extension study if they have successfully completed the 16 week treatment period ([redacted] titration and [redacted]

maintenance) in the current study and have not had a serious or severe adverse event (AE) that, in the investigator's opinion, was related to study treatment and would make it unsafe for the subject to continue study treatment dosing. For subjects electing to enroll in the active extension study, the last study visit will occur at the end of the maintenance period, and the first visit of the active extension study will occur at the same visit.

A complete schedule of assessments is provided in the study protocol.

3.1. Randomization

On Day 1, eligible subjects will return to the study center for collection of baseline safety and efficacy assessments. Subjects who continue to be eligible for the study will then be randomized 1:1 (NBI-921352:placebo) via an interactive web response system.

3.2. Data Monitoring Committee

Ongoing review of unblinded safety and tolerability data will be conducted by the independent DMC using reports provided by an independent statistical center. The DMC has the overall responsibility of safeguarding the interests of the subjects by monitoring data obtained in the study and making appropriate recommendations based on the reported data, thus ensuring that the study is being conducted with high scientific and ethical standards.

The DMC may review the efficacy data to assess the benefit-risk profile.

A review of the unblinded Sentinel Cohort data (including safety, tolerability, and PK data [PK data will only be assessed at [redacted] will be conducted by the DMC once the Sentinel Cohort titration period has completed.

3.3. Blinding

This is a double-blind, placebo-controlled study during which the subject, parents/caregivers, investigator, and all study center personnel will be blinded to the subject's treatment. The Sponsor will be blinded except for supply chain personnel who are not involved in decisions regarding subject treatment.

The randomization code will be broken for an individual subject only if the subject is pregnant, experiences a serious adverse event (SAE) that the investigator feels cannot be adequately treated without knowing the subject's treatment assignment, or for regulatory reporting requirements. Documentation of the unblinding must be maintained. Blinding will be maintained unless unblinding is necessary for subject safety.

Members of the DMC and individuals who generate the DMC reports will be unblinded throughout the study.

3.4. Sample Size Considerations

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

[redacted]

Sentinel Cohort subjects (n=8) do not represent a sufficient sample size to detect statistical differences between NBI-921352 and placebo treatment groups in 28-day seizure rate reduction from baseline; therefore, preliminary efficacy data will not be assessed for the Sentinel Cohort alone.

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 treatment group, 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

Analyses will be based on the safety analysis set, which will include all subjects who receive at least 1 dose of study treatment.

4.3. General Definitions

4.3.1. Baseline Definition

The assessments collected at Day 1 prior to study treatment will serve as the baseline value for all assessments unless otherwise noted. If a Day 1 visit value is not available, then the last measurement collected prior to study treatment will serve as baseline.

4.3.2. 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 of study treatment. 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.

4.3.3. Early Termination Data

Early termination (ET) data collected at postbaseline unscheduled visits (if applicable) 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.

4.3.4. Handling of Missing Data

4.3.4.1. Start Dates for Adverse Events

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:

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

There will be no imputation for AE stop dates.

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 and were screened
- The following categories will be presented by treatment group and overall. The number of subjects randomized will serve as the denominator to calculate percentages.
  - Randomized but not treated
  - Received study drug
  - Completed study drug dosing
  - Discontinued study drug dosing, including reasons
  - Completed study
  - Discontinued study, including reasons

A listing of randomized subjects will be provided and will include subject ID, weight group, informed consent date, randomization date and randomized treatment group.

5.2. 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 important protocol deviations (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 participant's rights, safety, or well-being.

A summary of the number and percentage of all participants with IPDs by deviation category will be presented.

All major protocol deviations will be presented in a data listing and any that are classified as IPDs will be flagged in the listing.

5.3. Demographic and Baseline Characteristics

Demographics and select study baseline (ie, last measurement collected prior to the first dose of study drug) characteristics will be summarized descriptively by treatment group and overall, for all randomized subjects.

The following variables will be summarized:

- Demographics: age, age category [redacted] sex, ethnicity, race, country

- Baseline subject characteristics: height (cm), weight (kg), body mass index (kg/m^2)

6. INTERIM ANALYSIS

A review of the unblinded Sentinel Cohort data (including safety, tolerability, and PK data [PK data will only be assessed at [redacted] will be conducted by the DMC. Efficacy analyses will not be performed as part of this analysis.

The DMC will also conduct an ongoing review of safety and tolerability data for both the Sentinel and Main Cohorts. Provisions will be in place to maintain the blinding of Sponsor study personnel. The DMC charter will describe the responsibilities, timing of meetings, and data review procedures for the members to follow.

6.1. Pharmacokinetic Evaluation for Sentinel Subjects

Individual sentinel subject steady-state NBI-921352 peak observed plasma concentration (C_{max}) and area under the curve from time zero to 8 hours postdose ($AUC_{(0-8)}$) values at [redacted] were determined using standard non-compartmental methods using reported plasma concentration values and nominal sample times.

The median NBI-921352 C_{max} and $AUC_{(0-8)}$ values were determined and provided to the DMC by an unblinded pharmacokineticist. The DMC reported to the Sponsor if the [redacted]

The interim analyses performed for the DMC will be described in the clinical study report and no additional summaries will be created.

7. SAFETY

Safety and tolerability of NBI-921352 in the Sentinel Cohort will be evaluated by assessment of treatment-emergent adverse events (TEAEs) and SAEs. Data from other safety evaluations (eg, vital signs, physical and neurological examinations, pubertal maturation staging, electrocardiograms, clinical laboratory assessments, Columbia-suicide severity rating scale) will not be summarized. Any abnormal results or significant changes from baseline will be assessed for AE reporting by the investigator and will be captured in the AE summaries.

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 by treatment group according to the 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.

7.1. Adverse Events

A TEAE is an AE with an onset date and time on or after the date of the first dose of study drug and within the 14 days after the date of the last dose of study drug. 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 4.3.4.1).

TEAEs, categorized by MedDRA system organ class (SOC) and/or preferred term (PT), will be summarized in frequency tables. The frequency tables will include the number and percentage of unique subjects experiencing each event one or more times by treatment group.

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, TEAE leading to study drug withdrawn, 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 by treatment group. 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 adverse event categories:

- TEAEs, classified by SOC and PT
- Any TEAEs, classified by PT, displayed in a descending order by frequency in the NBI-921352 group
- Treatment-emergent SAEs by SOC and PT
- TEAEs leading to study drug withdrawn by SOC and PT
- TEAEs leading to study discontinuation by SOC and PT
- TEAEs leading to death by SOC and PT

Separate listings of TEAEs resulting in study drug dose reductions, SAEs, and fatal AEs will also be provided. In the event that no subjects experience study drug dose reductions, SAEs, or

fatal AEs, 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.

8. 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.

9. DEVIATIONS FROM PROTOCOL PLANNED ANALYSIS

Study enrollment was paused after enrollment of the Sentinel Cohort to allow pre-specified DMC interim review of the safety, tolerability, and PK data from the Sentinel Cohort. [redacted] Enrollment was not re-opened, and the Sponsor decided to terminate the study.

The clinical study report will be synoptic in consideration of the ICH E3 Structure and Content of Clinical Study Reports. Therefore, this SAP includes selected safety, tolerability, and PK data from the Sentinel Cohort only; preliminary efficacy data will not be analyzed. Additionally, analyses mentioned in the protocol for the Main Cohort are not included as this cohort was not enrolled.