Statistical Analysis Plan (SAP)

NBI-98854-TD4020; AMENDMENT 1.0; 29 JANUARY 2024

A PHASE 4, SINGLE-ARM, OPEN-LABEL STUDY TO EVALUATE THE EFFECTIVENESS OF VALBENAZINE ON PATIENT- AND CLINICIAN-REPORTED OUTCOMES IN SUBJECTS WITH TARDIVE DYSKINESIA

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V2.0, 10 Jan 2025 for Protocol NBI-98854-TD4020.

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MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	04Mar2024	[redacted]	Not Applicable – First version
2.0	10Jan2025	[redacted]	• Added Evaluable Analysis Set [EVL] to Analysis Sets section • Updated [redacted] and [redacted] derivations • Added Topline Analysis to Planned Analyses section • Added Valbenazine Dose Category and Severity Category to Examination of Subgroups section • Updated demographics and other baseline characteristics, medical history, prior and concomitant medications, TDIS, SDS, EQ-VAS, PGI-C, CGI-TD-S, AIMS, and TEAE sections to include repeat tables by valbenazine dose category and/or severity category. • “AIMS total score” language has been changed to “AIMS Items 1-7 total score” for clarity • Added section 16 (Work/School During Study) • Updated definition of subgroup category of baseline severity

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1. ABBREVIATIONS

Abbreviation	Term
AE	Adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification
BARS	Barnes Akathisia Rating Scale
BMI	Body mass index
[redacted]	[redacted]
BUN	Blood Urea Nitrogen
CGI-TD-C	Clinical Global Impression of Change – Tardive Dyskinesia
CGI-TD-S	Clinical Global Impression of Severity – Tardive Dyskinesia
CI	Confidence interval
[redacted]	[redacted]
C-SSRS	Columbia-Suicide Severity Rating Scale
CTMS	Clinical Trial Management System
CK	Creatine Kinase
CYP	Cytochrome P450
DBL	Database Lock
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
ENR	Enrolled Subjects Set
EOS	End of Study
EOW	End of Study Week
EQ-5D-5L	5-level EQ-5D version
EQ-VAS	EQ-visual analog scale
ET	Early Termination
EVL	Evaluable Analysis Set
FAS	Full Analysis Set
FU	Follow-Up
GGT	Gamma-glutamyl transferase

Abbreviation	Term
HRQOL	Health-related quality of life
IP	Investigational Product
MDD	Major Depressive Disorder
MedDRA	Medical Dictionary for Regulatory Activities
MINI	Mini International Neuropsychiatric Interview
[redacted]	[redacted]
NBI	Neurocrine Biosciences, Inc.
PD	Protocol Deviation
PGI-C	Patient Global Impression of Change
PRO	Patient-Reported Outcomes
PT	Preferred Term
qd	Once a day
QOL	Quality of life
QTcF	Corrected QT interval using Fridericia's formula
RW	Real World
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SAS	Simpson-Angus Scale
SD	Standard deviation
SDS	Sheehan Disability Scale
SE	Standard Error
SOC	System Organ Class
TD	Tardive Dyskinesia
TDIS	Tardive Dyskinesia Impact Scale
TEAE	Treatment Emergent Adverse Event
WBC	White Blood Cell
WHO	World Health Organization
[redacted]	[redacted]

2. INTRODUCTION

This statistical analysis plan (SAP) describes the rules and conventions to be used in the presentation and analysis of effectiveness and safety. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This SAP is based on protocol amendment version 1.0, dated 29Jan2024 and Case Report Forms (CRFs) 5.0, dated 25Nov2024.

3. STUDY OBJECTIVES

3.1 Primary Objective

The primary objective is to evaluate patient-reported change in impacts of tardive dyskinesia (TD), social and work impairment, and overall health in subjects with TD who are receiving valbenazine for up to 24 weeks.

3.2 Secondary Objective

The secondary objective is to evaluate clinician-reported change in TD severity and patient-reported change in TD symptoms for subjects with TD who are receiving valbenazine for up to 24 weeks.

4. STUDY DESIGN

4.1 General Description

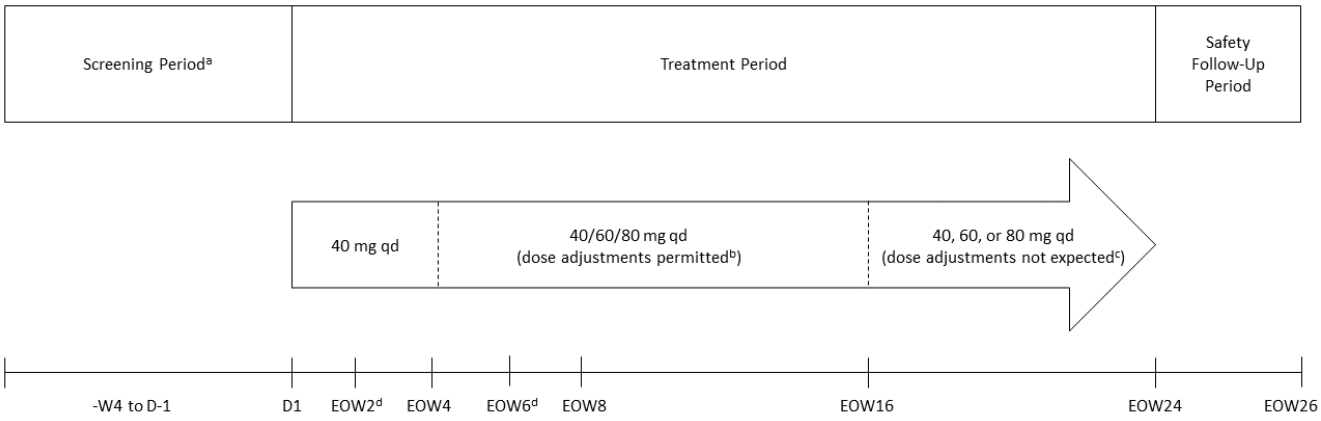
This is a Phase 4, single-arm, open-label study to evaluate the effectiveness of valbenazine on patient- and clinician-reported outcomes assessing health-related quality of life (HRQOL), functioning, and treatment effect in subjects with TD who are receiving valbenazine for up to 24 weeks.

Approximately 60 medically stable adult subjects (≥18 years of age) with schizophrenia, schizoaffective disorder, bipolar disorder, or major depressive disorder (MDD) who have neuroleptic induced TD of at least mild severity and who have awareness of and are experiencing at least mild distress from their abnormal movements will be enrolled.

Enrolled subjects will receive valbenazine orally once a day (qd) at 40, 60, or 80 mg during the study.

The study includes a Screening Period of up to 4 weeks, a 24-week Treatment Period, and a 2 week posttreatment Safety Follow-Up Period.

Figure 1: Study Design Schematic



D=study day; EOW=end of study week; qd=once a day; W=study week

[a] The Screening Period may be extended by up to 14 days for certain unavoidable circumstances (such as the COVID-19 pandemic) with approval from Sponsor or designee. Subjects who do not meet entry criteria during the Screening Period may be considered for rescreening 1 time with the approval of the Sponsor or designee.

[b] From the end of Week 4 visit until the end of Week 16 visit, dose adjustments may be performed based on individual treatment needs, response, and/or tolerability.

[c] From Week 17 until the end of Week 24, dose adjustments are not expected; however, dose decreases are permitted if needed for safety or tolerability.

[d] These are virtual visits (ie, telephone contacts). Tolerability and adherence will be assessed to determine whether an unscheduled onsite visit is needed.

4.2 Schedule of Events

The schedule of assessments can be found in Appendix A of the protocol (copied below).

Procedure	**Screening Period[a] (≤4 weeks)**	**Baseline**	**Treatment Period (24 weeks)**						**Safety Follow-Up (14 days after last dose)**
Study Week (Study Day)	**W-4 to D-1**	**D1**	**EOW2 (D15)**	**EOW4 (D29)**	**EOW6 (D43)**	**EOW8 (D57)**	**EOW16 (D113)**	**EOW24 (D169) / ET**	**EOW26 (D183)**
Visit Window	**N/A**	**N/A**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Onsite Visit	X	X		X		X	X	X	X
Virtual Visit			X		X				
Informed consent	X								
Inclusion/exclusion criteria	X	update							
Medical history[b]	X	update							
Demographics	X								
Medication history	X	update							
Concomitant medications	X	X	X	X	X	X	X	X	X
Physical examination[c]	X							X	
Vital signs (blood pressure, pulse, and body temperature)	X	X		X		X	X	X	
12-lead ECG[d]	X							X	
Pregnancy test[e]	X (s)	X (u)		X (u)		X (u)	X (u)	X (u)	X (u)
Serum prolactin	X							X	

Procedure	Screening Period[a] (≤4 weeks)	Baseline	Treatment Period (24 weeks)						Safety Follow-Up (14 days after last dose)
Study Week (Study Day)	**W-4 to D-1**	**D1**	**EOW2 (D15)**	**EOW4 (D29)**	**EOW6 (D43)**	**EOW8 (D57)**	**EOW16 (D113)**	**EOW24 (D169) / ET**	**EOW26 (D183)**
Visit Window	**N/A**	**N/A**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Onsite Visit	X	X		X		X	X	X	X
Virtual Visit			X		X				
FSH (postmenopausal women only)	X								
Clinical laboratory tests[f]	X							X	
Urine drug screen[g]	X								
Blood sample for CYP2D6 genotyping	X								
Blood sample for PK								X	
AIMS[h]	X (v)[i]	X		X		X	X	X	
CGI-TD-S[j]		X		X		X	X	X	
CGI-TD-C[j]				X		X	X	X	
PGI-C[j]				X		X	X	X	
EQ-5D-5L and EQ-VAS[j]		X		X		X	X	X	
TDIS[j]		X		X		X	X	X	
SDS[j]		X		X		X	X	X	
[redacted]									
C-SSRS Baseline/Screening Version	X								
C-SSRS Since Last Visit Version		X		X		X	X	X	X
BARS	X	X				X		X	
Modified SAS	X	X				X		X	
[redacted]									
Study treatment dosing at home[k]			X (D1 to D169)						
Dispense study treatment[l]		X		X		X	X		
Study treatment accountability[m]				X		X	X	X	
AE monitoring	X	X	X	X	X	X	X	X	X

AE=adverse event; AIMS=Abnormal Involuntary Movement Scale; BARS=Barnes Akathisia Rating Scale; [redacted] CGI-TD-C=Clinical Global Impression of Change - Tardive Dyskinesia; CGI-TD-S=Clinical Global Impression of Severity – Tardive Dyskinesia; COVID-19=coronavirus disease 2019; [redacted] C-SSRS=Columbia-Suicide Severity Rating Scale; CYP=cytochrome P450; D=study day; ECG=electrocardiogram; EOW=end of study week; EQ-5D-5L=5-level EQ-5D version; EQ-VAS=EQ-visual analog scale; ET=early termination; FSH=follicle-stimulating hormone; MDD=major depressive disorder; MINI=Mini International Neuropsychiatric Interview; [redacted] N/A=not applicable; PGI-C=Patient Global Impression of Change; PK=pharmacokinetic(s); qd=once a day; QTcF=corrected QT interval using Fridericia's formula; (s)=serum; SDS=Sheehan Disability Scale; SAS=Simpson-Angus Scale; TDIS=Tardive Dyskinesia Impact Scale; (u)=urine; (v)=video recorded; W=study week; [redacted]

If an unscheduled onsite is needed, the following assessments are required: vital signs (blood pressure, pulse, and temperature), concomitant medications, AE monitoring, C-SSRS Since Last Visit Version, and study treatment accountability.

[a] The Screening Period may be extended by up to 14 days for certain unavoidable circumstances (such as the COVID-19 pandemic) with approval from the Sponsor or designee. Subjects who do not meet entry criteria during the Screening Period may be considered for rescreening 1 time with the approval of the Sponsor or designee.

[b] The MINI will be used to assess the presence of moderate or severe substance use disorder as outlined in exclusion criterion #**Error! Reference source not found.**. If a subject is unable to confirm their psychiatric diagnosis (i.e., schizophrenia or schizoaffective disorder, bipolar disorder, or MDD) as outlined in inclusion criterion #**Error! Reference source not found.**, then the applicable module of the MINI will be used at screening to evaluate the presence of psychiatric disorders in order to assess the appropriateness of the subject for inclusion.

[c] Height will be measured at screening only. Height and weight will be measured with subjects not wearing shoes; and weight will be measured with subjects not wearing outerwear (e.g., jackets or coats).

[d] A standard 12-lead ECG will be conducted in triplicate (obtained at least 3 minutes apart and within a total time of 15 minutes) after the subject has rested supine for at least 5 minutes. The ECG parameters that will be assessed include heart rate, QT, QTcF, and PR intervals, and QRS duration based on the ECG machine readings (QTcF may need to be calculated).

[e] Pregnancy tests are required for females of childbearing potential; the urine pregnancy test result on Day 1 will be used to confirm eligibility.

[f] Clinical laboratory tests include hematology, chemistry, and prolactin. All blood samples will be obtained under nonfasted conditions.

[g] The urine drug screen will be performed at screening and may be repeated at any time at the investigator's clinical judgment.

[h] The AIMS examination will be administered by the investigator (or designee) in accordance with the AIMS administration procedure. At the specified visits, the AIMS administration will be video recorded (approximately 10 minutes) following standardized guidelines. If possible, the same person should administer the AIMS for an individual subject at all time points. At each scheduled assessment, the AIMS should be the first procedure to be administered. Each time the AIMS is administered, a single onsite AIMS rater (i.e., the study investigator or designee) will score AIMS Items 1 to 10 and complete AIMS Items 11 to 12.

[i] An external AIMS reviewer will assess the overall severity of dyskinesia based on a video recording of the screening visit. This assessment will be performed to confirm the TD severity required for study entry as outlined in inclusion criteria #**Error! Reference source not found.** and #**Error! Reference source not found.**.

[j] After the AIMS assessment has been completed, the TDIS, SDS, EQ-5D-5L [including the EQ-VAS], PGI-C, CGI-TD-S, CGI-TD-C, [redacted] should be performed before any other study procedures or assessments.

[k] On Days 1 to 169, valbenazine will be self-administered qd. Valbenazine can be taken with or without food and should be taken at approximately the same time every day. It is recommended that subjects take valbenazine at the same time as their oral antipsychotic medication(s), if appropriate.

[l] After the end of Week 4, if the investigator determines that a dose decrease is needed at an unscheduled onsite visit, then the subject will return all unused study treatment and receive a bottle of valbenazine at the new dose at this visit.

[m] Subjects will return all unused study treatment, and a compliance check will be performed by counting the capsules returned at each study visit.

4.3 Sample Size Considerations

The sample size for this open-label, single-arm study is not based on power calculations, but on clinical and logistical considerations. Assuming that 74% of subjects complete the Week 24 assessments, approximately 60 subjects will be enrolled to achieve a total of 44 subjects for the primary analysis. For example, for the primary endpoint of change from baseline in Tardive Dyskinesia Impact Scale (TDIS) at Week 24, a sample size of 44 subjects will provide a 2-sided 95% confidence interval (CI) that extends 2.5 from the observed mean, assuming that the standard deviation (SD) is known to be 8.55 and the CI is based on the large sample Z statistic. In a Neurocrine Biosciences, Inc. (NBI) sponsored open-label study of subjects with neuroleptic induced TD and either schizophrenia/schizoaffective disorder or mood disorder who received valbenazine for 48 weeks (Study NBI-98854-1402 [KINECT 4]), the change from baseline at Week 24 in TDIS ranged from -6.3 to -11.1 depending on valbenazine dose and disease category, with an SD of approximately 8.55.

To ensure adequate representation of subjects with different background psychiatric disorders and ranges of TD severity, subjects with schizophrenia or schizoaffective disorder will not exceed 50%

of the enrolled study population, and subjects with mild dyskinesia will not exceed 50% of the enrolled study population.

4.4 Changes to Analysis from Protocol

In protocol section 11.5.1.2 Primary Endpoints, there is this language:

> "Descriptive statistics (including both categorical variable statistics [using response categories (to be defined in SAP)] and continuous variable statistics [using numerical scores]) will be presented for change from baseline…".

There is only initial evidence that could be used to define highly exploratory categorical response category analyses. For this reason, these analyses will not be completed.

5. PLANNED ANALYSES

5.1 Interim Analysis

No interim analyses are planned.

5.2 Topline Analysis

A topline analysis will be performed after the planned database lock (DBL). Planned topline analyses identified in this SAP will be performed by IQVIA Real World (RW) Biostatistics following sponsor authorization of this SAP and DBL.

5.3 Final Analysis

One final analysis after DBL is planned. Planned analyses identified in this SAP will be performed by IQVIA RW Biostatistics following Sponsor Authorization of this SAP and DBL.

6. ANALYSIS SETS

6.1 Enrolled Subjects Set [ENR]

The Enrolled Subjects Set (ENR) will contain all subjects who provided informed consent for this study and met screening criteria.

6.2 Full Analysis Set [FAS]

The Full Analysis Set (FAS) includes all enrolled subjects with at least one baseline efficacy data point for any measure (considered primary, secondary, or other endpoints) and at least one postbaseline efficacy data point for any measure (considered primary, secondary, or other endpoints). Note that there is one FAS for all efficacy analyses. The FAS will be used for all

efficacy analyses. Subjects will be analyzed regardless of adherence to study treatment administration.

6.3 Safety Analysis Set [SAF]

The Safety Analysis Set (SAF) will include all enrolled subjects who take at least 1 dose of study treatment.

6.4 Evaluable Analysis Set [EVL]

The Evaluable Analysis Set [EVL] will include all subjects from the full analysis set who do not meet any of the following criteria:

1. EQ-visual analog scale (EQ-VAS) score of 100 at Day 1
2. TDIS score of 0 at Day 1
3. Sheehan Disability Scale (SDS) score of 0 at Day 1

The EVL will be used for sensitivity analysis of the primary efficacy endpoints. The rationale for this sensitivity analysis is that subjects in the EVL do not have room for improvement in either EQ-VAS, TDIS, or SDS scores.

7. GENERAL CONSIDERATIONS

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, SD or standard error (SE), minimum, and maximum for continuous and ordinal categorical variables. Number and percentage of subjects will be summarized for categorical variables.

All relevant 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.

All raw data will be included in listings including pre-treatment, posttreatment, and unscheduled visits. ENR will be used for disposition, protocol deviations (PD), primary clinical diagnosis, demographics, baseline characteristics, and efficacy listings. SAF will be used for all other listings. The listings will indicate which subjects are excluded from analysis sets, as applicable (FAS, SAF). In addition, the listings will contain study, day and any total score calculations needed for efficacy endpoints. Listings will not contain any imputed values for missing data.

See Appendices 1 and 2 for programming conventions and handling of partial dates, respectively.

7.1 Baseline

For analysis purposes, unless otherwise specified, the assessment collected on Day 1 (first dose date) will serve as the baseline value for all assessments. If a Day 1 visit value is not available, then the last measurement collected prior to study drug dosing will serve as baseline. The screening visit may be conducted anytime up to 28 days prior to first dose.

7.2 Windowing Conventions

Study day is calculated relative to the first dose date. If date is prior to first dose date, derivation is (Date minus First dose date). If date is after first dose date, then derivation is (Date minus First dose date +1). Based on this calculation we have the below. Note that there is no Study Day 0.

- First dose date = day 1
- Days prior to first dose date = [-x, -1]
- Days after first dose date = [2, x]

The visit number for each visit, including scheduled, unscheduled, repeat, and early termination/end of study (EOS) visits, will be re-mapped based on the actual study day according to Table 1. If multiple measurements occur within the same visit window after mapping, the non-missing measurement that is closest to the target study day will be used for the summary tables where one observation per visit is needed, unless otherwise specified. Where there are ties between the earlier and later observation within the visit window, the earlier non-missing observation will be used. Note that all data from scheduled, unscheduled, repeat, and ET/EOS visits, although not included in the analysis tables based on the visit window algorithm, will be provided in the listings.

Table 1: Analysis Visit Windows

Scheduled Visit	Target Day	Analysis Window (Study Day Range, Inclusive)
Baseline*	1	≤-1 or 1 *Note there is no Day 0 based on definition
Week 2	15	[2, 22]
Week 4	29	[23, 36]
Week 6	43	[37, 50]
Week 8	57	[51, 64]
Week 16	113	[65, 141]
Week 24/EOT	169	[142, 176]
Safety FU (0-6 days after last dose) *Treatment still in system	N/A - There should not be a visit here. However, if there is, we need to have a window to allow for it.	[Date of last dose, Date of last dose +6]

Safety FU (7-21 days after last dose) *Treatment out of system	Date of last dose + 14	[Date of last dose+7, Date of last dose +21]

EOT: end of treatment; FU: follow-up.
*Note that if a Day 1 visit value is not available, then the last measurement collected prior to study drug dosing will serve as baseline (see section 7.1).

7.3 Common Calculations

Change from baseline is calculated as the postbaseline value minus the baseline value; a negative value will represent a decrease at the postbaseline visit. Percent change from baseline is calculated as [(postbaseline value – baseline value)/baseline value*100]. If either the baseline or postbaseline value is missing, the change from baseline and/or percent change from baseline will also be missing.

7.4 Software Version

All analyses will be conducted using SAS® software version 9.4 or higher.

8. STATISTICAL CONSIDERATIONS

8.1 Statistical Tests and Confidence Intervals

Unless otherwise specified in the description of the analyses, a two-sided 95% CI will be considered as a default (alpha= 5%). CIs for the mean will be calculated based on a normal distribution, and CIs for proportions will be calculated using the exact binomial method (Clopper-Pearson). No confirmatory testing or p-values are planned because this is a single-arm descriptive study.

8.2 Missing Data

Missing data will not be imputed unless specified in the specific endpoint section.
Partial date handling for Treatment Emergent Adverse Events (TEAE) and Prior/Concomitant Medications is described in Appendix 2.

8.3 Examination of Subgroups

There will be 3 subgroups of interest. The main subgroup of interest is disease category. All analyses will be presented overall and by disease category. The second subcategory is valbenazine dose level, which will be assessed for demographics and other baseline characteristics, medical history, prior and concomitant medications, TDIS, SDS, EQ-VAS, Patient Global Impression of Change-Tardive Dyskinesia (PGI-C), Clinical Global Impression of Severity – Tardive Dyskinesia (CGI-TD-S), Abnormal Involuntary Movement Scale (AIMS) items 1–7 total

score, Item 8 and Responder, and summary presentations of TEAEs by system organ class (SOC) and preferred term (PT). The third subcategory is TD severity, which will be assessed for demographics, TDIS, SDS, EQ-VAS, and AIMS Items 1–7 total score. Definitions are below:

1. Disease Category (Based on Primary Clinical Diagnosis electronic case report form (eCRF) at screening):
    - Schizophrenia or schizoaffective disorder
    - MDD or bipolar disorder
2. Valbenazine Dose Category (Based on dosage patient is taking at end of Week 16)
    - 40 mg
    - 60 mg
    - 80 mg
    - Missing
        - A missing category will be designated for subjects who leave the study prior to Week 16 or are otherwise missing Week 16 dose information.
3. Severity Category (Based on AIMS Item 8 score at baseline)
    - < Mild (defined as a score of 0 or 1)
    - Mild (defined as a score of 2)
    - >Mild (defined as a score of 3 or 4)
    - Missing

8.4 Randomization Schedule

No randomization will be performed for this study as it is a single-arm study.

9. OUTPUT PRESENTATIONS

Appendix 1 shows conventions for presentation of data in outputs.

The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary Tables, Listings, and Figures (TLFs) to be provided by IQVIA RW Biostatistics.

10. DISPOSITION AND WITHDRAWALS

The summary of subject enrollment and disposition will include the items described below and will be presented overall and by disease category subgroups. This will be part of the topline analysis.

- The total number of subjects who were screened.
- The total number of subjects who met screening criteria / ENR.

- The following categories will be presented. The number of subjects in the ENR will serve as the denominator to calculate percentages.
    - Completed EOS Week (Week 24) visit, as defined by Week 24 eCRF
    - Completed Safety Follow-Up visit (Scheduled for Week 26 or 14 after last dose of drug)
    - Completed study, as defined at EOS page in the eCRF
    - Discontinued study, including reasons for discontinuation

The number of subjects in each analysis set will be presented overall and by disease category subgroups. In addition, specific endpoint N's mentioned below will also be presented.

- Screened subjects
- ENR
- FAS
- SAF
- Primary Endpoints:
    - Number of subjects with baseline and Week 24 TDIS total score
    - Number of subjects with baseline and Week 24 SDS Item1
    - Number of subjects with baseline and Week 24 SDS Item2
    - Number of subjects with baseline and Week 24 SDS Item3
    - Number of subjects with baseline and Week 24 EQ-VAS score

11. PROTOCOL DEVIATIONS

PDs will be tracked through Clinical Trial Management System (CTMS). A summary of the number and percentage of subjects with major PDs (subject-level) by deviation category will be provided. Categories listed below:

- Eligibility and entry criteria
- Informed consent
- Visit criteria
- Concomitant medication criteria
- Study procedures criteria
- AE
- Investigational product (IP) conditions
- IP Administration
- Study procedures criteria

A specific subcategory of IP Administration about dose compliance will also be summarized:

- The number and percent of subjects <80% dose-compliant will be summarized at the end of the study.

All major subject-level PDs will be presented in a data listing as well.

12. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic and baseline characteristics data will be summarized using descriptive statistics for continuous variables, and frequency counts and percentages for categorical variables. Demographics will be presented based on the SAF overall, by disease category subgroups, by valbenazine dose subgroups, and by TD severity subgroups. Demographic tables performed overall, by disease category, and by TD severity will be included as part of topline analyses. Other baseline characteristics will be presented overall, by disease category subgroups, and by valbenazine dose subgroups. Other baseline characteristics tables overall and by disease category will be part of the topline analysis. The following demographic and other baseline characteristics will be reported for this study:

- Demographics:
  - Age (years) at screening
  - Sex
  - Race
  - Ethnicity
- Other Baseline Characteristics:
  - Weight (kg)
  - Height (cm)
  - Body mass index (BMI) (kg/ m^2)
    - BMI (kg/ m^2) = weight (kg)/ height $(m)^2$
  - Baseline TDIS total score (details in section 16.1.1.1)
  - Baseline SDS Item 1, 2, 3 (details in section 16.1.1.2)
  - Baseline EQ-VAS score (details in section 16.1.1.3)
  - Baseline Cytochrome P450 (CYP)2D6 Genotyping

13. MEDICAL HISTORY

The medical history data will be summarized descriptively for the SAF overall, by disease category subgroups and by valbenazine dose subgroups . Medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 26.0). The medical history 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 SOC and PT levels. The table will be sorted alphabetically by SOC and then, within a SOC, by PT in descending order of frequency. If a subject has multiple medical histories coded to one PT, the subject is only counted once.

14. PRIOR AND CONCOMITANT MEDICATIONS

Prior medications and concomitant medications will be presented for the SAF overall, by disease category subgroups, and by valbenazine dose subgroups. Medications will be coded by the World Health Organization (WHO) Drug Dictionary and summarized by Anatomical Therapeutic Chemical Classification (ATC) Level 3 category (or Level 2 if there is not an applicable Level 3 category) and preferred name.

Medications will be defined as either prior or concomitant based on the medication start and stop dates relative to study drug dosing.

- Prior medications: Medications that were started and stopped prior to the date of the first dose of study drug will be assigned to the prior period only
- Concomitant medications:
    - Medications that started prior to the first dose of study drug and either stopped during the study after first dose or indicated as “ongoing”, or
    - Medications that started on or after the first dose date of study drug.

The number and percentage of subjects using medications in each WHO Drug ATC category (Level 3/preferred name) will be summarized. A subject may take the same medication more than once or multiple medications for a subject may be classified under the same ATC level or preferred name. A subject is counted only once for each level of medication classification within a summary. See Appendix 2 for handling of partial dates for medications. In the case where it is not possible to define a medication as prior or concomitant, the medication will be classified conservatively as concomitant.

15. STUDY MEDICATION EXPOSURE AND DOSING COMPLIANCE

15.1 Study Medication Exposure

Duration of exposure will be summarized with descriptive statistics for the SAF overall by disease category subgroups. In addition, it will be summarized by dose level and by CYP2D6 genotype metabolizer status. The duration of exposure to study drug will be calculated as: (last dose date – first dose date) +1. Categorical summaries will also be presented for duration of exposure categories. The summary will display the number and percentage of the subjects who take at least

1 dose. In addition, the number and percentage of subjects will be presented by the categories listed below separately and cumulatively, based on visits and target days. See below:

Separately	**Cumulatively**
<2 weeks (<14 days)	< 2 weeks (<14 days)
2 weeks to <4 weeks (14-27 days)	≥2 weeks (≥14 days)
4 weeks to <6 weeks (28-41 days)	≥4 weeks (≥28 days)
6 weeks to <8 weeks (42-55 days)	≥6 weeks (≥42 days)
8 weeks to <16 weeks (56-111 days)	≥8 weeks (≥56 days)
16 weeks to <24 weeks (112-167 days)	≥16 weeks (≥112 days)
≥24 weeks (≥168 days)	≥24 weeks (≥168 days)

A summary of exposure categories by dose level (40mg, 60mg, 80mg, any dose) will also be provided. The daily dose level prescribed is entered directly in the exposure eCRF. Overall exposure by dose level will be based on the number of days that a specific dose was taken. Overall exposure by dose level will be calculated as: sum [(last dose date – first dose date) +1] for each dose level. Gaps in exposure within a dose level or between dose changes will not be counted as exposure in this summary.

Example 1: if a subject was first on 40mg, then switched to 60mg, and then switched backed to 40mg after a 15-day gap, then the calculation will be as follows:

- Dose details:
  - Dose1: 40mg, start date=date1, stop date=date2
  - Dose2: 60mg, start date=date2+1day, stop date=date3
  - Dose3: 40mg, start date=date3+15days, stop date=date4
- Exposure derivations:
  - Any dose: [date4 – (date3+15) +1] + [date3 – date1 +1]
  - 40mg: [date4 – (date3+15) +1] + [date2 – date1 +1]
  - 60mg: date3 – (date2+1) +1

Note that the 15-day gap is not included as exposure.

Example 2: if a subject was on 40mg the entire study, but had a 12-day gap in the middle, then the calculation will be as follows:

- Dose details:
  - Dose1: 40mg, start date=date1, stop date=date2
  - Dose2: 40mg, start date=date2+12day gap, stop date=date3
- Exposure derivations:
  - Any dose: [date3 – (date2+12) +1] + [date2 – date1 +1]

- 40mg: [date3 – (date2+12) +1] + [date2 – date1 +1]

Note that the 12-day gap is not included as exposure.

The general rules to be applied for this table are listed below:

- Column headings will be: 40mg, 60mg, 80mg, any dose.
- Exposure categories will be: as listed above.
- The same subject may appear in multiple dose level categories and duration rows within the table but will only be counted once in the “any dose” column.

The number of subjects who received study drug over time will be summarized with descriptive statistics. The summary will also display the number and percentage of the subjects at each dose level (40, 60, and 80 mg) by visit.

15.2 Dosing Compliance

Subject non-compliant dosing intervals (<80% of expected doses) were identified as dosing compliance PDs tracked through CTMS. The number and percent of subjects <80% dose-compliant will be summarized at the end of the study in the PD summary table.

15.3 Valbenazine Plasma Concentrations

Mean plasma concentrations at Week 24/ET of valbenazine and its major metabolite will be summarized descriptively overall and by disease category subgroups. In addition, it will be presented by the last dose level at Week 24 or ET.

16. EFFICACY OUTCOMES

16.1 Primary Efficacy

16.1.1 Primary Efficacy Variables & Derivations

16.1.1.1 Tardive Dyskinesia Impact Scale (TDIS)

- The TDIS is a disease specific patient-reported outcome that assesses the impact of impairment and disability associated with dyskinesia. It defines impact of TD in terms of 6 dimensions: Mouth/Throat Function (3 items), Dexterity (2 items), Mobility (2 items), Emotional (2 items), Pain (1 item), and Social (1 item). Each item measures the impact of dyskinetic movements in terms of difficulty or frequency over the last 7 days on a 5-point scale, with scores ranging from 0 to 4. Response options for the difficulty items range from not at all (0) to extremely (4); those for the frequency items range from never (0) to all of the time (4). The TDIS total score is the sum of the scores of TDIS Items 1 to 11. Scores can

range from 0 to 44, with higher scores representing greater TD impact. If any of the items are missing, total score will be set to missing.

- **Primary Endpoint:** Change from baseline in the TDIS total score at Week 24.
- **Variables/Derivation:** Change from baseline at Week 24 is defined as Week 24 total score – Baseline total score.

16.1.1.2 Sheehan Disability Scale (SDS)

The SDS is a patient-reported measure of functional impairment used in a number of psychiatric disorders to measure the effect of treatment on disability. It includes 3 self-rated items designed to measure how work, social life, and family life are impaired by current psychiatric symptoms. Each item includes an 11-point analog scale that uses visual-spatial, numeric, and verbal descriptive anchors to represent the degree of disruption from 0 (none at all) to 10 (extremely). It also assesses the number of days a subject was unable to work/attend school and the number of days a subject was underproductive in the past week. The SDS total score is the sum of the 3 impairment items and will only be calculated for subjects who rate all 3 items.

- **Primary Endpoint:** Change from baseline in the SDS Items 1, 2, and 3 at Week 24.
- **Variables/Derivations:** Change from baseline at Week 24 is calculated for each of the 3 impairment items separately.
  - W24 Item 1 score – Baseline Item 1 score.
  - W24 Item 2 score – Baseline Item 2 score.
  - W24 Item 3 score – Baseline Item 3 score.

To limit the impact of missing item-level data, the SDS will be modified as follows: Functional impairment in the domain of work (Item 1) will be imputed with a score of 10 for participants who were not able to work for reasons related to TD. This modification and analysis will be performed solely by Neurocrine Biosciences Inc or designate.

16.1.1.3 EQ-Visual Analog Scale (EQ-VAS)

- Subjects rate their overall health on a 0 to 100 hash-marked, vertical EQ-visual analog scale (EQ-VAS).
  - **Primary Endpoint:** Change from baseline in the EQ-VAS score at Week 24.
  - **Variables/Derivation:** Change from baseline at Week 24 is defined as Week 24 rating – Baseline rating.

16.1.2 Primary Analysis of Primary Efficacy Variable(s)

The primary objective of this study is to evaluate patient-reported change in impacts of TD, social and work impairment, and overall health in subjects with TD who are receiving valbenazine for up to 24 weeks. The primary efficacy analyses will be performed using the FAS overall, by disease category subgroups, by valbenazine dose subgroups, and by TD severity subgroups. In addition, sensitivity analyses using the EVL overall and by disease category subgroups will be performed. Primary efficacy analyses performed overall, by disease category, and by TD severity will be included as part of topline analyses.

For the FAS and EVL analysis sets, descriptive statistics (including both categorical variable statistics [categories defined below as quartiles] and continuous variable statistics (mean, SD, median, Q1, Q3, min, max) [using numerical scores]) will be presented for change from baseline in the TDIS total score, SDS Items 1, 2, and 3, and EQ-VAS at the end of Week 24. Two-sided 95% CIs (normal approximation) will be included in descriptive statistics for changes from baseline.

In addition, box-plots assessing the distribution of scores at each visit overall, by disease category subgroups, by valbenazine dose subgroups, and by TD severity subgroups will be presented for the FAS only.

Quartiles of change from baseline for each of the primary endpoints separately (TDIS total score, SDS Item1, SDS Item2, SDS Item3, and EQ-VAS at Week 24) will be presented overall and by disease category subgroups for the FAS.

16.2 Secondary Efficacy

16.2.1 Secondary Efficacy Variables & Derivations

16.2.1.1 Patient Global Impression of Change-Tardive Dyskinesia (PGI-C)

- In the PGI-C, subjects will rate the change in their TD symptoms from the initiation of study treatment dosing by choosing one of 7 responses (very much improved, much improved, minimally improved, not changed, minimally worse, much worse, and very much worse).
    - **Secondary Endpoint:** PGI-C response at Week 24.
    - **Variable/Derivation:** This variable is the response at Week 24.

16.2.1.2 Clinical Global Impression of Severity – Tardive Dyskinesia (CGI-TD-S)

- The CGI-TD-S is a 7-point scale (1=normal, not at all ill, not at all ill, 2=borderline ill, 3=mildly ill, 4=moderately ill, 5=markedly ill, 6=severely ill, 7=among the most extremely ill

patient) rating the overall global severity of TD. The investigator or qualified study site personnel will rate the scale at the scheduled times.

- **Secondary Endpoint:** Change from baseline in the CGI-TD-S score/response at Week 24.
- **Variables/Derivation:** Change from baseline at Week 24 is defined as the Week 24 rating – Baseline rating.

16.2.1.3 Abnormal Involuntary Movement Scale (AIMS)

- The severity of TD will be assessed using the AIMS rating scale. The AIMS includes a total of 12 items. The score for Items 1 through 7 ranges from 0 (no dyskinesia) to 4 (severe dyskinesia) and includes facial and oral movements (Items 1 to 4), extremity movements (Items 5 to 6), and trunk movements (Item 7). Items 8, 9, and 10 rate global judgments: Items 8 (severity of abnormal movements) and 9 (incapacitation due to abnormal movements) scores range from 0 (none, normal) to 4 (severe) and Item 10 is scored based only on the subject's report of his/her awareness of abnormal movements from 0 (no awareness) to 4 (aware, severe distress). Items 11 and 12 are yes/no questions concerning problems with teeth and/or dentures. The AIMS Items 1–7 total score is defined as the sum of the scores of AIMS Items 1 through 7. The AIMS Items 1–7 total score can therefore range from 0 to 28, with higher scores indicating greater severity. If any of the 7 items have a missing value, the total score for that subject/visit will be set equal to missing.
  - **Secondary Endpoint:** Change from baseline in the AIMS Items 1–7 total score at Week 24.
  - **Variables/Derivation:** Change from baseline at Week 24 is defined as Week 24 total score – Baseline total score.

16.2.2 Analysis of Secondary Efficacy Variables

The secondary objective is to evaluate clinician-reported change in TD severity and patient-reported change in TD symptoms for subjects with TD who are receiving study drug for up to 24 weeks. The secondary efficacy analyses for PGI-C, CGI-TD-S, and AIMS Item 8 will be performed overall, by disease category subgroups, and by valbenazine dose subgroups using the FAS. The secondary efficacy analyses for AIMS Items 1–7 total score will be performed overall, by disease category subgroups, by valbenazine dose subgroups, and by TD severity subgroups using the FAS. AIMS Items 1–7 total score analyses performed overall, by disease category, and by TD severity will be included as part of topline analyses. Descriptive statistics for the PGI-C response (categorical) and change from baseline in the CGI-TD-S score (both continuous and categorical)

and the AIMS Items 1–7 total score (continuous) will be presented. Two-sided 95% CIs (normal approximation) will be included in the descriptive statistics for changes from baseline. In addition, box-plots (for continuous measures) and bar charts (for PGI-C), assessing the distribution at each visit overall and by disease category will be presented.

16.3 [redacted]

16.3.1 [redacted]

16.3.1.1 [redacted]

[redacted]

16.3.1.2 [redacted]

[redacted]

16.3.1.3 [redacted]

[redacted]

16.3.1.4 [redacted]

[redacted]

[redacted]

16.3.1.5 [redacted]

[redacted]

16.3.1.6 [redacted]

[redacted]

16.3.1.7 Primary Efficacy (TDIS, SDS, EQ-VAS) at all Timepoints

- Primary Efficacy Endpoints at all timepoints:

- Change from baseline in the TDIS total score at all timepoints, change from baseline in the SDS individual items at all timepoints, change from baseline in the EQ-VAS score at all timepoints.
- See section 16.1 for details.

16.3.1.8 Secondary Efficacy (PGI-C, CGI-TD-S, AIMS) at all Timepoints

- Secondary Efficacy Endpoints at all timepoints:
  - PGI-C response at all timepoints, change from baseline in CGI-TD-S score at all timepoints and AIMS Items 1–7 total score at all timepoints.
  - See section 16.2 for details.

16.3.2 [redacted]

[redacted]

16.3.3 Work/School during study

Subject work and/or school status from study start through the EOS will be assessed at the end of the study visit. Frequencies and percentages of the following items will be summarized overall and by disease category subgroups for the FAS:

- Subject working for pay or attending school at start of study (Yes, No, Missing)
  - Reasons for not working for pay or attending school (Medical condition or TD, Subject on disability pay, Other, Missing)
- Subject working or school status changed anytime during study (Yes, No, Missing)
  - Number and percentage of subjects with work or school status improved
    - Amount of improvement (Very little, A lot, Missing)
    - Reason for improvement (Medical condition or TD improved, Able to get job/take classes that better suited needs, Missing)
  - Number and percentage of subjects with work or school status worsened
    - Amount of worsening (Very little, A lot, Missing)

- Reason for worsening (Medical condition or TD got worse, lost job or stopped taking classes because of medical condition or TD, Retired because of medical condition or TD)

17. PATIENT-REPORTED OUTCOMES (PRO) AND CLINICIAN-REPORTED OUTCOMES

Most PROs and clinician-reported outcomes are described in section 16. Some additional analyses are listed below.

17.1.1 PRO and Clinician-Reported Outcomes Variables & Derivations

17.1.1.1 [redacted]

[redacted]

17.1.2 Analysis of PRO and Clinician-Reported Outcome Variables

The additional analyses of PRO and Clinician-Reported outcomes will be performed using the FAS overall and by disease category subgroups. AIMS responder analyses will be performed using the FAS overall, by disease category subgroups, and by valbenazine dose subgroups. Descriptive statistics will be presented. Two-sided 95% CIs (normal approximation) will be included in the descriptive statistics for changes from baseline and for percent of subjects responding.

18. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the SAF.

18.1 Adverse Events

Adverse Events (AEs) will be coded using MedDRA central coding dictionary, Version 26.0.
A TEAE is an AE not present prior to the initiation of study drug dosing or is an already present event that worsens either in intensity or frequency following the initiation of study drug dosing. See protocol section 10, for further details on defining a TEAE.

The number and percentage of unique subjects experiencing each TEAE at least once during the study will be presented. Subjects will be counted only once for multiple events that code to the same MedDRA coded term. Unless otherwise specified, summary tables will include events with a start date on or after the date of the first dose of study drug and up to the last dose of study drug + 14 days.

An AE overview summary table will be provided which summarizes the number and percentage of subjects with any TEAE, any TEAE leading to dose reduction, any TEAE leading to study drug discontinuation, any serious TEAE, any TEAE leading to death. In addition, the maximum TEAE severity (mild, moderate, severe) reported for each subject and the closest relationship to the study medication (not related, unlikely, possible, definitely) reported for each subject will be summarized with frequencies and percentages.

Two versions of the primary TEAE frequency tables will be presented overall and by valbenazine dose category:

- Frequency of TEAEs by SOC and PT, with SOCs sorted alphabetically and PTs within each SOC sorted by decreasing frequency (number of unique subjects).
- Frequency of TEAEs by PT, with PT sorted by decreasing frequency (number of unique subjects).

These 2 versions presented overall will be part of topline analyses.

In addition, tables will be provided for posttreatment emergent events (AE start dates after last dose of study drug to the date of the last dose of study drug + 14 days) and non-treatment emergent AEs (AE start dates after last dose date + 14 days) separately. The events will be summarized and presented by PT within SOC.

See Appendix 2 for handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case, i.e. treatment emergent.

Listings will include TEAEs and Non-TEAEs.

18.1.1 TEAEs Leading to Discontinuation of Study Medication

TEAEs leading to permanent discontinuation of study medication will be identified by using the AE CRF, Action Taken with Study Drug = “Drug Withdrawn”. Summary tables of TEAEs leading to discontinuation of study drug will be presented. The number and percentage of subjects with a TEAE leading to study drug discontinuation will be presented by PT within SOC (presented in the same method as the primary TEAE table). More than one AE can contribute to study drug

discontinuation per subject. The first line of the table will display the number and percentage of subjects with at least one TEAE leading to study drug discontinuation.

A listing of TEAEs leading to study drug discontinuation will be provided which includes subject identification number (ID), last dose received prior to the onset time of the TEAE(s) leading to discontinuation, study day of the discontinuation, and other relevant information from the AE eCRF. Note that "last dose received prior to the onset time of the TEAE[s] leading to discontinuation" reflects the actual dose level received prior to the AE.

18.1.2 TEAEs Leading to Study Drug Dose Reductions

TEAEs leading to dose reduction of study medication will be identified by using the AE CRF, Action Taken with Study Drug = "Dose Reduced". Summary tables of TEAEs leading to study drug dose reductions will be presented. The number and percentage of subjects with a TEAE leading to a dose reduction will be presented by PT within SOC (presented in the same method as the primary TEAE table). More than one AE can contribute to a dose reduction per subject. The first line of the table will display the number and percentage of subjects with at least one TEAE leading to dose reduction.

A listing of TEAEs leading to study drug dose reduction will be provided which includes subject ID, last dose received prior to the onset time of the TEAE(s) leading to study drug dose reduction, and other relevant information from the AE eCRF. Note that "last dose received prior to the onset time of the TEAE[s] leading to study drug dose reduction" reflects the actual dose level received prior to the AE.

18.1.3 Serious Adverse Events (SAEs)

Serious adverse events (SAEs) are those events recorded as "Serious" on the AE page of the eCRF. A summary table of SAEs will be presented. The table will include the frequency of SAEs presented by PT within SOC (presented in the same method as the primary TEAE table). This will be included in the topline analysis.

A listing of SAEs will be provided and will include subject ID, last dose received prior to the onset time of the SAE, study day of the SAE, and all additional relevant information from the AE eCRF.

18.1.4 Adverse Events Leading to Death

TEAEs leading to death are those events which are recorded as "Fatal" on AEs page of the (e)CRF. A summary table of TEAEs leading to death will be presented. The table will include the frequency of SAEs presented by PT within SOC (presented in the same method as the primary TEAE table).

A listing of TEAEs leading to death will be provided and will include subject ID, last dose received prior to the onset time of fatal TEAE, study day of the fatal TEAE, and any additional relevant information from the AE eCRF.

18.1.5 Non-Serious Adverse Events

Non-serious AEs are those events not recorded as “Serious” on the AEs page of the eCRF. A summary table of non-serious AEs will be presented. The tables will include the frequencies presented by PT within SOC (presented in the same method as the primary TEAE table).

18.2 Laboratory Evaluations

The following safety laboratory parameters will be analyzed using the SAF:

- Hematology: complete blood count including white blood cell (WBC) 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, mean platelet volume.
- Clinical Chemistry: sodium, potassium, calcium, magnesium, phosphorus, chloride, blood urea nitrogen (BUN), bicarbonate, creatinine, uric acid, albumin, alkaline phosphatase, lactate dehydrogenase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), creatine kinase (CK), total bilirubin, total protein, and glucose.
- Prolactin.

The hematology, clinical chemistry, and prolactin data will be summarized with descriptive statistics at baseline and at each scheduled postbaseline visit. Both observed values and changes from baseline will be summarized.

18.2.1 Laboratory Reference Ranges

Shift tables will be presented for selected clinical laboratory variables based on the reference range-based categories of “Low,” “Normal,” or “High.” A clinical laboratory variable value will be assigned to one of these 3 categories according to the reference ranges provided by the central clinical laboratory. The shift tables will present the shift from baseline to Week 24 using observed values. Each shift table will have 3 rows and 3 columns, with rows reflecting the reference range category at baseline, and columns reflecting the reference range category at Week 24. A “Total” row and “Total” column will also be included. Subjects with a missing baseline value or who do not have Week 24 data will be excluded from the shift 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. Shift tables will be presented for the following clinical laboratory variables:

- AST in U/L,
- ALT in U/L,
- GGT in U/L,
- total bilirubin in mg/dL,
- CK in U/L,
- creatinine in mg/dL,
- prolactin in ng/mL,
- BUN in mg/dL,
- WBC in 10^3/µL,
- hemoglobin in g/dL, and
- platelet count in 10^3/µL.

18.3 Vital Signs

The vital signs data will be summarized with descriptive statistics at baseline and at each postbaseline visit among the SAF. Both observed values and changes from baseline will be summarized. The following vital signs data will be included in the analysis:

- systolic and diastolic blood pressure (supine) (mmHg),
- systolic and diastolic blood pressure (standing) (mmHg),
- orthostatic systolic and diastolic blood pressure (mmHg),
    - calculated as standing value minus supine value
- pulse rate (beats/min),
- respiratory rate (breaths/ min),
- body temperature (overall – combining all method: oral, forehead, ear, rectum) (^{0} C),
- height (cm) (only measured at screening),
- weight (kg), and
- BMI (kg/m^2).

18.4 Electrocardiogram (ECG)

The quantitative ECG variables will be summarized with descriptive statistics at baseline and at each scheduled postbaseline for the SAF. Both observed values and changes from baseline will be summarized. Frequency counts and percentages for the ECG interpretation variable categories will be summarized at each scheduled visit.

- Quantitative: The triplicate values of the quantitative ECG variables (heart rate, PR interval, QRS duration, QT interval, and corrected QT interval using Fridericia's formula [QTcF]) measured at each visit will be averaged for the purpose of analysis. If less than 3 values are recorded at an assessment, then the average of the available value(s) will be used.
- Categorical: Investigator's assessment of the ECG as "Normal", "Abnormal, not Clinically Significant", or "Abnormal, Clinically Significant". This presentation will be included as part of the topline analysis.

Categorical summaries will also be presented for the QTcF interval data. For these summaries, a subject's highest reported postbaseline value (including values reported at unscheduled visits) will be used to determine in which category(s) the subject will be counted. The averaged triplicate values will be used when determining each subject's highest reported values.

Two categorical summaries will be presented for the QTcF intervals. For the first summary, the number and percentage of subjects whose highest reported QTcF postbaseline value meets the following thresholds will be summarized:

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

The second categorical summary will display the number and percentage of subjects whose largest QTcF increase from their baseline value meets the following thresholds:

- Greater than 30 msec
- Greater than 60 msec

18.5 Other Safety Assessments

18.5.1 Barnes Akathisia Rating Scale (BARS)

- The BARS is a validated 4-item scale to assess the presence and severity of drug-induced akathisia. This scale includes both objective items (e.g., observed restlessness) and subjective items (e.g., subject's awareness of restlessness and related distress), together with a global assessment of akathisia. Objective akathisia, subjective awareness of restlessness and subjective distress related to restlessness are rated on a 4-point scale from 0 – 3 and are summed yielding a total score ranging from 0 to 9. Global assessment is made on a 6-point scale of 0 to 5 (0=absent; 1=questionable; 2=mild akathisia; 3=moderate akathisia; 4=marked akathisia; 5=severe akathisia). The BARS total score and BARS global assessment of akathisia score will be summarized descriptively by visit both

continuously and categorically. This will be presented for the SAF overall and by disease category subgroups.

- Note that if any of the objective or subjective items are missing the total score will be set to missing as well.

18.5.2 Modified Simpson-Angus Scale (SAS)

- The SAS is a clinician-administered rating scale that has been used to assess antipsychotic-induced parkinsonism in clinical practice and research settings. The present study uses a modified 10-item version of the SAS (for the screening and Day 1 assessment of eligibility) in which “Leg Pendulousness” and “Head Dropping” items included in the original version have been replaced with “Head Rotation” and “Akathisia,” and has been used frequently in schizophrenia clinical trials. Each item is rated using a 5-point scale (0-4); the modified total SAS scores can range from 0 to 40. Total scores will be summarized descriptively by visit for the SAF overall and by disease category subgroups.
- Note that if any of the items are missing total score will be set to missing as well.

18.5.3 Columbia-Suicide Severity Rating Scale (C-SSRS)

- The C-SSRS is a validated instrument to prospectively assess suicidal ideation and behavior. There are versions of the questionnaire designed for use at screening (Baseline/Screening version) and at baseline and visits throughout the study (Since Last Visit 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. Of note, the Since Last Visit version of the C-SSRS will be administered at baseline and visits throughout the study, but the lookback period will be since the last C-SSRS assessment, not since the subject’s last visit. The C-SSRS will be administered and scored by the investigator or qualified study site personnel.
- The C-SSRS summary will be assessed with the SAF overall and by disease category subgroups. The 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 (not reported for the Screening/past 1 year assessment)
        - (6) Preparatory acts or behavior
        - (7) Aborted attempt
        - (8) Interrupted attempt
        - (9) Non-fatal suicide attempt
            - When actual lethality is not marked as death
        - (10) Completed suicide
            - When actual lethality is marked as death
    - Suicidal Behavior Category: Any of items (6) through (10)
    - Suicidal Ideation or Behavior Category: Any of items (1) through (10)
- In this summary, each subject's C-SSRS 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 the worst postbaseline suicidal ideation scores to baseline scores will be presented. The shift table scores are defined as the following:
    - 0 = No suicidal ideation (defined when "Wish to be Dead" and "Non-Specific Active Suicidal Thoughts" items are both selected as "No")
    - 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. Subjects missing either a baseline score or all postbaseline scores will not appear in the table.

18.5.4 Caregiver Assessments

[redacted]

[redacted]

19. REFERENCES

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Mazza, G.L., Enders, C.K., and Ruehlman, L.S. (2015). Addressing item-level missing data: a comparison of proration and full information maximum likelihood estimation. Multivariate Behavioral Research, 50(5): 504-519.

Streiner, D.L., Norman, G.R., and Cairney, J. (2024). Health measurement scales: a practical guide to their therapeutic development and use. Oxford University Press.

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

- End of study week (EOW) xx will be labeled as Week xx in TLF output.
- Decimal Precision:
    - Summary statistics will be presented using the following decimal precision (i.e., 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, standard deviation (SD) and standard error (SE) will have one more decimal place than the data being summarized; and the number of observations (n) and the sample size (N) will be reported as an integer. Percentages other than 0 or 100% will be reported to one decimal place (percentages for zero counts are omitted and 100% is reported as 100%). Confidence intervals (CIs) for means will be reported to the same number of decimal places as mean values; and confidence intervals for percentages will be reported to one decimal place. This rule may be modified if warranted, based on practical considerations.

APPENDIX 2. PARTIAL DATE CONVENTIONS

Missing and incomplete ("partial") dates for Adverse Events (AEs) and concomitant medications will be imputed for the purpose of estimating the timing of the event or medication usage in relationship to study drug. Any data listings will display the original dates as reported in the database. Imputed dates will NOT be presented in the listings.

As noted in section 18, to handle missing/partial start dates for AEs, investigators will be asked to respond "Yes" or "No" on the eCRF as to whether the AE started after the subject took the first dose of study drug. An AE with a response of "Yes" will be classified as a TEAE. If the investigator's response is missing, then the treatment emergent status will be derived based on the AE onset date and time relative to the date and time of the subject's first dose of study drug.

The missing and incomplete ("partial") dates for AEs will be imputed using the following algorithm.

- Start date:
  - Missing day - impute the 1st of the month unless the same month and year as the study drug, otherwise impute the first dose date of study drug;
  - Missing day and month - impute 1st January, unless the same year as the study drug, otherwise impute the first dose date of study drug.
- Stop date:
  - There will be no imputation for AE stop dates.

To handle missing/partial dates for prior and concomitant medications, the following algorithm will be employed to estimate the time of medication usage relative to study drug.

- Start date:
  - Missing day - impute the 1st of the month, or if the same month and year as the study drug impute the first dose date of study drug;
  - Missing day and month - impute 1st January, of if the same year as the study drug impute the first dose date of study drug.
- Stop date:
  - Missing day - impute the last day of the month, or if the same month and year as the study drug impute the last dose date of study drug;
  - Missing day and month - impute 31st December, or if the same year as the study drug impute the last dose date of study drug.

- Note if any of the above imputation results in a start date that is later than an existing (not imputed) stop date for the event, the start date will be imputed as the stop date. . If any of the above imputations result in a stop date that is earlier than an existing (not imputed) start date for the event, the stop date will be imputed as the start date.

APPENDIX 3. [redacted]

[redacted]

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Status: Completed
Subject: Complete with Docusign: Neurocrine TD4020 SAP Text V2 10Jan2025.docx
Source Envelope:
Document Pages: 43
Signatures: 3
Certificate Pages: 5
Initials: 0
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[redacted] Security Level: Email, Account Authentication (None)	[redacted] Signature Adoption: Pre-selected Style Using IP Address: [redacted]	Sent: 1/10/2025 8:46:17 PM Viewed: 1/21/2025 6:23:40 PM Signed: 1/21/2025 6:23:47 PM
Electronic Record and Signature Disclosure: Accepted: 1/21/2025 6:23:40 PM ID: [redacted]		
[redacted] Security Level: Email, Account Authentication (None)	[redacted] Signature Adoption: Pre-selected Style Using IP Address: [redacted]	Sent: 1/10/2025 8:46:16 PM Viewed: 1/14/2025 10:28:22 AM Signed: 1/14/2025 10:30:20 AM
Electronic Record and Signature Disclosure: Accepted: 10/16/2024 10:01:05 AM ID: [redacted]		
[redacted] Security Level: Email, Account Authentication (None)	[redacted] Signature Adoption: Pre-selected Style Using IP Address: [redacted]	Sent: 1/10/2025 8:46:16 PM Viewed: 1/10/2025 8:46:29 PM Signed: 1/10/2025 8:46:37 PM
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In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

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Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	1/10/2025 8:46:17 PM
Certified Delivered	Security Checked	1/10/2025 8:46:29 PM
Signing Complete	Security Checked	1/10/2025 8:46:37 PM
Completed	Security Checked	1/21/2025 6:23:47 PM

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