STATISTICAL ANALYSIS PLAN
PHASE 3B

VERSION 1.0

DATE OF PLAN:

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STUDY DRUG:

NBI-98854

PROTOCOL NUMBER:

NBI-98854-1506

STUDY TITLE:

OPEN-LABEL ROLLOVER STUDY FOR CONTINUING VALBENAZINE (NBI-98854) ADMINISTRATION FOR THE TREATMENT OF TARDIVE DYSKINESIA

SPONSOR:

Neurocrine Biosciences, Inc.

12780 El Camino Real

San Diego, CA 92130

Telephone: (858) 617-7600

CONFIDENTIAL

SIGNATURE PAGE

This document has been prepared by:

[redacted] 19Oct2017

<<Printed Name>>, Project Statistician Signature Date
Neurocrine Biosciences, Inc.

This document has been reviewed and accepted by:

[redacted] 18 Oct 2017

<<Printed Name>>, <<Title>> CMO Signature Date
Neurocrine Biosciences, Inc.

[redacted] 10/19/17

<<Printed Name>>, <<Title>> CRO Signature Date
Neurocrine Biosciences, Inc.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification
BPRS	Brief Psychiatric Rating Scale
CGI-TD	Clinical Global Impression of Tardive Dyskinesia
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	Electrocardiogram
eCRF	Electronic case report form
ET	Early termination
FDA	[United States] Food and Drug Administration
GGT	Gamma-glutamyl transferase
IPD	Important protocol deviation
MedDRA	Medical Dictionary for Regulatory Activities
n, N	Sample size (number of subjects)
NBI	Neurocrine Biosciences, Inc.
PCS	Potentially clinically significant
PSQ	Patient satisfaction questionnaire
PT	Preferred term
Qd	Once daily
QTcF	Fridericia's correction of QT interval
SAE	Serious adverse event
SAP	Statistical Analysis Plan
[redacted]	[redacted]
SD	Standard deviation
SEM	Standard error of the mean
SFS	Social Functioning Scale
SOC	System organ class
TEAE	Treatment-emergent adverse event
TD	Tardive dyskinesia

Abbreviation	Term
UBACC	University of California, San Diego Brief Assessment of Capacity to Consent
UDS	Urine drug screen
ULN	Upper limit of normal
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) provides a detailed description of the tables, figures, and listings that will be prepared to summarize the data from the Phase 3b study described in Neurocrine Biosciences, Inc. (NBI) Protocol NBI-98854-1506.

2. STUDY OBJECTIVES

The objectives of this study are:

- To provide continued access to valbenazine for the treatment of tardive dyskinesia (TD) in approximately 150 subjects with schizophrenia, schizoaffective disorder or mood disorder who have completed a Phase 3 valbenazine study.
- To collect long-term safety and tolerability data in subjects receiving valbenazine (40 mg or 80 mg) administered once daily for up to 72 weeks (18 months).

3. STUDY DESIGN

3.1. Study Design Overview

This rollover study will provide subjects who completed a Phase 3 valbenazine study open-label access to valbenazine for the treatment of TD until valbenazine is anticipated to be available commercially or they complete 72 weeks of treatment. In addition, this study is designed to collect long-term safety and tolerability data as well as subject-reported information following chronic administration of valbenazine in subjects with TD.

This is a rollover study with open-label, fixed-doses of valbenazine (40 mg qd or 80 mg qd) for a total of up to 72 weeks of treatment. This study will allow enrollment of approximately 150 medically stable male and female subjects with TD who had previously participated in and completed the NBI-98854-1304 or NBI-98854-1402 Phase 3 study. Subjects can have their final NBI-98854-1304 or NBI-98854-1402 visit on the same day as Day 1 for this rollover study provided they sign the current study's informed consent before the final NBI-98854-1304 or NBI-98854-1402 visit. This will allow certain safety assessments to be used for both studies. The safety assessment results that can apply to both studies include physical examinations (including weight), vital signs, and electrocardiograms (ECG). Other Day 1 assessments (including safety labs) must be collected for the current study (even if the subject is completing the final visit for the previous study). The study will be conducted in approximately 40 centers in the US.

On Day 1, eligible subjects will receive a supply of valbenazine 40 mg qd for the first 4 weeks of the treatment period. On Day 2, valbenazine will be administered at home in the morning or evening. After Day 2, the subject will be directed to take their dose at about the same time each day (eg, morning or evening).

At the end of Week 4, the investigator may escalate the subject's dose to 80 mg qd or continue with the subject's current dose (40 mg qd). A dose escalation will be allowed at the end of

Week 4 based on the physician investigator's (or designee's) assessments of the safety and tolerability of valbenazine as well as clinical impression of TD.

At any time after dose escalation, the investigator may decrease the dose to 40 mg if the subject is unable to tolerate the dose increase. The subject will continue at this dose (40 mg) until the end of the treatment period (end of Week 72). Subjects who are unable to tolerate the starting dose of 40 mg or the resumption of 40 mg will be discontinued from the study. If treatment is interrupted for ≤5 missed consecutive doses, subjects are allowed to resume with their current dose regimen (40 mg qd or 80 mg qd). If treatment is interrupted for >5 missed consecutive doses, subjects should contact the investigator before resuming treatment; subjects deemed clinically stable by the investigator may resume with their current dose regimen (40 mg qd or 80 mg qd).

Subjects will return to the clinical site every 4 weeks for assessments and dispensation of valbenazine. Subjects who do not want to continue in the study will be terminated from the study. The final assessments will be performed at the end of Week 72 or early termination.

3.2. Summary of Study Assessments

Efficacy:

- Clinical Global Impression of TD-severity (CGI-TD-severity) will be completed by the investigator at baseline (Day 1) and at the end of Weeks 12, 24, 36, 48, 60, and 72 or upon early termination.

Safety:

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

- Adverse events.
- Clinical laboratory tests (hematology, clinical chemistry, and urinalysis).
- Serum prolactin.
- Vital signs (including orthostatic blood pressure and pulse).
- Physical examinations.
- 12-lead electrocardiogram.
- Suicidal ideation and behavior – evaluated using the Columbia-Suicide Severity Rating Scale (C-SSRS).

Additional assessments:

- Patient Satisfaction Questionnaire (PSQ) will be completed by the subject at baseline (Day 1) and at the end of Weeks 12, 24, 36, 48, 60, and 72 or upon early termination.
- The Social Functioning Scale (SFS) will be completed by the subject at baseline (Day 1) and at the end of Weeks 12, 24, 36, 48, 60, and 72 or upon early termination.

4. STUDY ASSESSMENT SCHEDULE

The schedule of study assessments is provided in Table 1.

Table 1: Schedule of Assessments

Procedure	Baseline	Open-Label Valbenazine Treatment Period																		
Week[a]	Day 1[b]	DAY 2	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72/ET[c]
Visit[a]	1		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Informed consent/ UBACC	X																			
Inclusion/exclusion criteria	X																			
Medical and surgical history	X																			
Physical examination (including weight)	X				X			X			X			X			X			X
Height	X																			
Vital signs	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead electrocardiogram[d]	X		X		X			X			X			X			X			X
Pregnancy test[e]	X (S,U)		X (U)	X (U)	X (U)	X (U)	X (U)	X (U)	X (U)	X (U)	X (U)	X (U)	X (U)	X (U)	X (U)	X (U)	X (U)	X (U)	X (U)	X (U)
Clinical laboratory tests[f]	X				X			X			X			X			X			X
Urine drug screen[g]	X																			
Alcohol breath test	X																			
Serum prolactin	X				X			X			X			X			X			X
BPRS	X																			
C-SSRS[h]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CGI-TD-severity	X				X			X			X			X			X			X
Patient Satisfaction Questionnaire	X				X			X			X			X			X			X
Social Functioning Scale	X				X			X			X			X			X			X
Daily valbenazine dosing at home[i]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense valbenazine[j]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Valbenazine accountability[k]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event monitoring	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior and concomitant medications	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Outpatient clinic visit	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations and footnotes appear on the following page.

Definitions: BPRS=Brief Psychiatric Rating Scale; CGI-TD-severity=Clinical Global Impression of Tardive Dyskinesia-Severity; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ET=early termination; QTcF=corrected QT interval using Fridericia's formula; S=serum; U=urine; UBACC=University of California, San Diego Brief Assessment of Capacity to Consent.

[a] The visits after Day 1 will have a visit window of -7 or +2 days.
[b] For subjects completing the final NBI-98854-1304 or NBI-98854-1402 visit on the same day as Day 1, the NBI-98854-1304 or NBI-98854-1402 assessments for physical examination (including weight), vital signs, and ECG will be used for Day 1.
[c] Final visit for subjects who complete the study (or early termination).
[d] A standard 12-lead ECG will be conducted after the subject has rested supine for at least 5 minutes. The ECG parameters that will be assessed include heart rate, QT interval, QTcF, PR interval, and QRS duration based on the ECG machine readings.
[e] Pregnancy tests are only required for female subjects who are not postmenopausal for at least 1 year prior to Day 1. Urine and serum pregnancy tests will be conducted at Day 1. The urine pregnancy test result on Day 1 will be used to confirm eligibility.
[f] Clinical laboratory tests include hematology, clinical chemistry, and urinalysis. All blood samples will be obtained under non-fasted conditions.
[g] Urine drug screen (UDS) collected on Day 1 will be analyzed by the central lab. In addition, a UDS kit provided by the central lab will be used at the clinical site to confirm eligibility on Day 1. A UDS using a kit provided by the central lab may be conducted at the clinical site at any time during the study if the subject is suspected of substance or drug abuse.
[h] The "Screening/Baseline" version should be used at baseline (Day 1) and "Since Last Visit" version should be used at all subsequent visits.
[i] Starting on Day 2, subjects will self-administer valbenazine daily (in the morning or evening, at approximately the same time each day) at home in the presence of their caregiver (if applicable).
[j] Subjects will receive a 4-week supply of valbenazine on Day 1 and will need to return to clinical site every 4 weeks to obtain a 4-week supply of valbenazine.
[k] At the end of Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, and 72 subjects will return all unused valbenazine, and a compliance check will be performed by counting the capsules returned at the visit.

5. STATISTICAL ANALYSES

5.1. General Statistical Procedures

Descriptive statistical methods will be used to summarize the data from this study. The term "descriptive statistics" refers to the number of subjects (n), mean, median, standard deviation (SD), standard error of the mean (SEM), minimum, and maximum for continuous variables; and refers to the number and/or percentage of subjects (or events) for categorical variables.

Unless stated otherwise, each table of descriptive statistics and associated figures will summarize data according to the following "treatment groups":

- Valbenazine 40 mg (subjects whose dose is not escalated to 80 mg at Week 4)
- Valbenazine 80 mg (subjects whose dose is escalated to 80 mg at Week 4 and maintained at that dose for the duration of the study)
- Valbenazine 80/40 mg (subjects whose dose is escalated to 80 mg at Week 4 and subsequently reduced to 40 mg at any time during the study)
- All subjects (this may also be referred to as "overall" in treatment groups specifications below)

Note that subjects who discontinue from the study prior to the Week 4 dose escalation visit will be included in the valbenazine 40 mg treatment group.

5.2. Sample Size

The sample size for this study is based on practical considerations and not on a statistical power calculation.

5.3. Pooling of Sites

With exception of the summary of subject enrollment by site, study sites will be pooled in all tables and graphs, since the majority of sites in this study are expected to enroll fewer than five subjects.

5.4. Handling of Early Termination Visit Data

An early termination (ET) visit occurs when a subject discontinues from the study prior to completing the scheduled Week 72 visit. For the purpose of data summarization, a visit window will be applied to account for ET visits. An ET visit will be mapped to Week 4 if it occurs within 7 days prior to and 6 days after the expected study day of the Week 4 visit. For scheduled study visits at Weeks 8 through 72, an ET visit will be mapped to the next scheduled study visit if it occurs within 14 days prior to and 13 days after the expected study day of the visit. Early termination visit data which are not mapped to a scheduled visit will be displayed in applicable by-subject data listings but not included in by-visit summaries. Note that all subjects enrolled in this study will have an ET visit as the study was ended early per sponsor request.

Table 2 displays the allowable study day range for each scheduled visit for ET visit mapping purposes.

Table 2: Allowable Study Day Range for Early Termination Visit Mapping

Scheduled Visit	Target Study Day	Time Interval (Study Day Range)
Week 4	28	21-34
Week 8	56	42-69
Week 12	84	70-97
Week 16	112	98-125
Week 20	140	126-153
Week 24	168	154-181
Week 28	196	182-209
Week 32	224	210-237
Week 36	252	238-265
Week 40	280	266-293
Week 44	308	294-321
Week 48	336	322-349
Week 52	364	350-377
Week 56	392	378-405
Week 60	420	406-433
Week 64	448	434-461
Week 68	476	462-489
Week 72	504	490 +

5.5. Handling of Missing Data

Missing values for outcome measures will not be replaced with imputed values except as noted above for the ET visit data mapped to scheduled visits for data summary purposes.

Missing and incomplete ("partial") dates for AEs and concomitant medications will be imputed only for the purpose of estimating the time of the event or medication usage in relationship to study treatment periods (eg, prestudy period vs. valbenazine treatment period); however, all data listings will display the original dates as reported on the eCRF.

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 of study drug;

If only the day component is missing from the date, the date will be imputed as the date of the first dose of study drug if the date is in the same month and year as the first dose of study drug; otherwise, the missing day component will be imputed as the first day of the month;

If both the day and month components are missing from the date, the date will be imputed as the date of the first dose of study drug if the date is in the same year as the first dose; otherwise, the missing components will be imputed as 01 January;

If any of the above imputations result in a start date that is later than an existing complete (not imputed) end date for the event, the start date will be set equal to the end date.

The imputation rules for concomitant medication start dates are as follows:

- If the date is completely missing, the date will be imputed as 01 January in the year of the subject's screening vital signs assessment;
- If only the day component is missing from the date, the date will be imputed as the date of the first dose of study drug if the date is in the same month and year as the first dose of study drug; otherwise, the missing day component will be imputed as the first day of the month;
- If both the day and month components are missing from the date, the date will be imputed as the date of the first dose of study drug if the date is in the same year as the first dose; otherwise, the missing components will be imputed as 01 January;
- If any of the above imputations result in a start date which is later than an existing complete (not imputed) medication stop date, the start date will be set equal to the stop date.

5.6. Coding Dictionary

Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 12.0). Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary.

5.7. Analysis Sets

The safety analysis set will be the single analysis set defined for this study. The safety analysis set will include all enrolled subjects who take at least one dose of study drug and have any data collected after the initial dose of study drug.

A summary of the number and percentage of subjects included in (and excluded from, as applicable) the safety analysis set will be provided for each treatment group. The number and percentage of subjects excluded from the safety analysis set by reason for exclusion will also be provided.

Summaries of subject enrollment and disposition, enrollment by study site, and analysis set inclusion/exclusion status will include all enrolled subjects. All other summaries will be based on the safety analysis set.

Individual subject listings of all available data will be provided for all enrolled subjects.

5.8. Subject Enrollment and Disposition

The summary of subject enrollment and disposition will display, by treatment group and overall (ie, "all subjects"), the number and percentage of subjects who enrolled in the study, who discontinued from the study prior to the sponsor early termination of the study, and who completed the study through the sponsor early termination of the study (note that no subjects completed the study through Week 72 due to the sponsor early termination of the study).

The table will also summarize the number and percentage of subjects who discontinued from the study prior to the sponsor early termination of the study according to reason for discontinuation.

A summary of enrollment by study site will be presented. This summary will display the number of subjects enrolled at each site, by treatment group and for all subjects, and will be presented by

disease category subgroup (schizophrenia/schizoaffective disorder or mood disorder) as well as with both disease category subgroups combined.

An additional table will display the number of subjects in each treatment group (and overall) who completed each study visit (note that this summary is based on the safety analysis set).

5.9. Important Protocol Deviations

Important protocol deviations (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. An assessment of IPDs will be performed by a committee composed of NBI Clinical Development project team members. Important protocol deviations may include, but are not limited to the following:

- Failure to obtain informed consent from the subject prior to performing any study procedures
- Deviations from key inclusion/exclusion criteria
- Use of prohibited concomitant medications
- Error in drug dispensing which results in a subject not receiving intended treatment
- Significant deviation from protocol-specified dosing regimen

The number and percentage of subjects with IPDs will be summarized by deviation category, treatment group, and for all subjects.

5.10. Demographics

Demographic data (age, gender, race, and ethnicity) will be summarized with descriptive statistics by treatment group and overall.

5.11. Baseline Subject Characteristics

The following baseline subject characteristics will be summarized with descriptive statistics by treatment group and overall:

- Weight (in units of pounds and kilograms)
- Height
- Body mass index
- Disease category (schizophrenia/schizoaffective disorder or mood disorder)
- Age at diagnosis of schizophrenia/schizoaffective disorder
- Age at diagnosis of mood disorder
- Age at diagnosis of tardive dyskinesia
- BPRS total score

5.12. Medical History

Medical history will be summarized in frequency tables (number and percentage of subjects) by MedDRA System Organ Class (SOC) and Preferred Term (PT) for each treatment group and overall.

5.13. Study Drug Dosing

5.13.1. Study Drug Dosing Compliance and Time of Dose

Study drug dosing compliance (defined as the subject having taken at least 80% of doses since their previous visit) and time of dose (daytime or nighttime) will be summarized by visit (beginning with Week 4). The number and percentage of subjects who were dose compliant and who dosed in each "time of dose" category will be summarized by treatment group and overall.

5.13.2. Dose Escalation at Week 4

The number and percentage of subjects whose dose was increased from 40 mg to 80 mg at Week 4 vs. maintained at 40 mg will be summarized. Then reason for dose maintenance at Week 4 (adverse event, clinical impression of TD, or "other") will also be summarized (number and percentage of subjects in each category). Note that this summary is not "by treatment group".

5.13.3. Dose Reductions after Week 4

The dose reduction summary will present the number of subjects with a dose reduction (from 80 mg to 40 mg) at any time during the study. The number of subjects with a dose reduction will displayed by dose reduction reason category (adverse event, clinical impression of TD, or "other").

Note that this summary is not "by treatment group".

5.14. Efficacy Assessments

5.14.1. Clinical Global Impression of Tardive Dyskinesia-Severity (CGI-TD-Severity)

5.14.1.1. CGI-TD-Severity Scores

Each of the seven CGI-TD-severity response categories will be assigned a numerical score as follows:

- Normal, not at all ill = 1
- Borderline ill = 2
- Mildly ill = 3
- Moderately ill = 4
- Markedly ill = 5
- Severely ill = 6
- Among the most extremely ill patient = 7

5.14.1.2. CGI-TD-Severity Descriptive Statistics

Descriptive statistics (including both categorical variable statistics [using response categories] and continuous variable descriptive statistics [using numerical scores]) will be presented by treatment group and overall for the CGI-TD-severity data at each visit.

Descriptive statistics for CGI-TD-severity scores and response categories will be presented also by disease category subgroup (schizophrenia/schizoaffective disorder or mood disorder).

Changes from baseline (Day 1) at each postbaseline visit will be included in the summaries of CGI-TD-severity numerical scores.

5.14.1.3. CGI-TD-Severity Responder Analysis

A subject will be classified as a CGI-TD-severity responder at a given visit if their score is equal to a "1" or a "2". The number and percentage of subjects classified as responders at each visit (including the baseline visit) will be summarized by treatment group. This summary will also be presented by disease category subgroup.

5.14.1.4. CGI-TD-Severity Graphs

Mean (±SEM) values of the CGI-TD-severity scores and changes from baseline at each visit will be summarized in line graphs by treatment group. Bar graphs of the percentage of subjects who are CGI-TD-severity responders will also be presented for each treatment group at each visit.

5.15. Safety Assessments

5.15.1. Adverse Events

5.15.1.1. Treatment-Emergent Adverse Event Frequency Tables

A treatment-emergent adverse event (TEAE) is an adverse event with an onset date on or after the date of the first dose of study drug.

TEAEs, categorized by MedDRA (Version 12.0) SOC and PT, will be summarized in frequency tables. TEAEs summarized by PT only will be presented also. Unless stated otherwise, the frequency tables will include the number of events reported, and the number and percentage of unique subjects experiencing each event one or more times during the study interval summarized in the table. A description of each summary table is provided below.

Adverse events with an onset date prior to the date of the first dose of study drug will be presented only a data listing.

<u>TEAEs Reported after Day 1 through Week 4 Visit</u>

TEAEs with an onset date during the first four weeks of the study (after Day 1 through Week 4) will be summarized separately from TEAEs that occur after the Week 4 visit, as all subjects receive the same dose of 40 mg during the first 4 weeks of treatment. These tables will therefore not be "by treatment" and will summarize data for all subjects as a single group.

Tables will be presented which include all TEAES, only TEAEs considered to be possibly or definitely related to study drug, and TEAEs categorized according to the maximum intensity reported for a given subject.

These TEAEs will also be presented by PT only (ie, not by SOC), with PTs sorted according to decreasing frequency of subjects reporting each event.

<u>TEAEs Reported after Week 4 Visit</u>

TEAEs with an onset date after Week 4 will be summarized by treatment group. This table will include a separate column for all subjects.

Similar tables will be presented including only TEAEs considered to be possibly or definitely related to study drug and categorizing TEAEs according to the maximum intensity reported for a given subject.

These TEAEs will also be presented by PT only (ie, not by SOC), with PTs sorted according to decreasing frequency of subjects reporting each event based on the "all subjects" column.

TEAES Reported at Any Time During Study

TEAEs reported at any time after Day 1 will be summarized in frequency tables similar to those described above for all subjects combined (ie, without regard to treatment group).

5.15.1.2. Adverse Event Overall Summaries

Overall summary tables will be provided which summarize the number and percentage of subjects with any TEAE, any treatment-related TEAE (ie, possibly or definitely related per electronic case report form [eCRF]), any severe TEAE, any TEAE leading to study discontinuation, any serious TEAE, and any TEAE resulting in death. An overall summary table will be presented for each of the study intervals described above in Section 5.15.1.1 and will include the same treatment group columns as in the frequency tables.

5.15.1.3. Adverse Events Resulting in a Study Drug Dose Reduction

A summary of TEAEs resulting in a study drug dose reduction (from 80 mg to 40 mg) will be presented. This summary table will display the PTs for the TEAEs resulting in a dose reduction, with the PTs sorted in order of decreasing frequency (based on number of subjects). The first line of the table will display the total number of subjects with a dose reduction.

A listing of TEAEs resulting in a study drug dose reduction will be included in the study report. This listing will include subject, study day of the dose reduction, and both the PT and reported term for all TEAEs that resulted in the dose reduction (note that the specific PTs resulting in a dose reduction are determined from the AE eCRF "action taken with study drug" field).

5.15.1.4. Adverse Events Resulting in Premature Study Discontinuation

Summary tables of TEAEs resulting in premature study discontinuation will be presented for the following study periods:

- After Day 1 through Week 4
- After Week 4

These summary tables will include both the SOC and PT, with data summarized by treatment group (for TEAEs occurring after Week 4) and overall. Note that the onset date of the TEAE(s) resulting in study discontinuation (not the date of discontinuation) will be the basis for determining the study period assignment.

A listing of TEAEs resulting in premature study discontinuation will be presented in the study report. The listing will include subject, treatment group, study period when the TEAE which resulted in study discontinuation occurred, study day of the TEAE onset, and both the PT and reported (verbatim) term for all TEAEs that resulted in the premature study discontinuation (note that this is determined from the AE eCRF "action taken" field).

5.15.1.5. Deaths and Other Serious Adverse Events

The frequency of SAEs will be summarized in tables using the approach described above for TEAEs resulting in study discontinuation. The table formats (which include both the SOC and PT) for the SAE tables will match those used for the TEAE discontinuation tables. Deaths will be presented in a listing only.

Listings of SAEs and deaths will be presented in the study report. These listings will include subject, treatment group, study period when the death or SAE occurred, study day of the death or SAE, and all other AE-specific information reported on the AE eCRF.

5.15.2. Clinical Laboratory Data

The hematology, clinical chemistry, and prolactin data at each visit will be summarized with descriptive statistics by treatment group and for all subjects. Both observed values and changes from baseline (Day 1) will be summarized.

The prolactin data will be summarized for each gender separately in addition to the summary described above.

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 three categories according to the reference ranges provided by the central clinical laboratory.

Each shift table will have three rows and three columns, with rows reflecting the reference range category at baseline, and columns reflecting the reference range category at the subject's final study visit. Subjects with missing data for a clinical laboratory variable at either timepoint will not be included in tables for that variable. The shift tables will be presented for each treatment group and for all subjects.

Shift tables will be displayed for the following clinical laboratory variables: AST, alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), total bilirubin, creatine kinase, creatinine, BUN, prolactin, hemoglobin A1c, white blood cell count, absolute neutrophil count, hemoglobin, and platelet count.

Summaries of sponsor-defined potentially clinically significant (PCS) values will be presented for the following clinical laboratory variables: ALT, AST, creatinine kinase, GGT, total bilirubin, white blood cell count, neutrophil count, creatinine, and BUN. The number and percentage of subjects with one or more PCS values at any time after Day 1 will be summarized by treatment group and for all subjects. Note that data collected at both scheduled and unscheduled study visits will be included in this assessment. The criteria for identifying PCS values are provided in Table 3.

Table 3: Potential Clinically Significant Criteria for Selected Clinical Laboratory Variables

Variable	PCS Threshold
ALT	>3 x ULN (upper limit of normal)
AST	>3 x ULN

Variable	PCS Threshold
Creatine kinase	>5 x ULN
GGT	>3 x ULN
Total bilirubin	>1.5 x ULN
White blood cell count	≤2.8 x 1000/µL
Absolute Neutrophil count	<1.5 x 1000/µL
Creatinine	>1.5 x Day -1 value or > 1.5 x ULN
BUN	>30 mg/dL (> 10.71 mmol/L)

A listing of all subjects with any PCS value will be presented in the study report. This listing will include the values of the clinical laboratory variables in Table 3 at all study visits for each subject with one or more PCS values. The listing will include subject, treatment group, visit, study day of visit, and all laboratory results for the analytes with a PCS value. Values that meet the PCS criteria will be flagged with an asterisk in the listing.

Scatter plots for prolactin will be created which display the subjects' final study visit values vs. baseline values. Each plot will include a 45 degree ("y=x") reference line. A separate plot will be generated for each treatment group and for all subjects.

The clinical laboratory data listings will include associated normal/reference ranges (if provided). In addition, values outside the normal range will be flagged as "L" if below the lower limit of normal and as "H" if above the upper limit of normal. There will also be a flag for clinical significance based on the investigator's assessment of out-of-range values. The urinalysis data will be presented in data listings only.

Repeat clinical laboratory samples may be collected at any time during this study due to either missing or abnormal results. The general rule of thumb for summarizing these data is to include the original sample results in summary tables and graphs. All sample results (original and repeat) will be included in data listings.

5.15.3. Physical Examination and Weight

Clinically significant physical examination findings will be presented by subject and visit in a listing. The listing will include subject, treatment group, visit at which the finding was reported, study day of the visit, and the clinically significant finding.

Body weight, which is measured during the physical examination, will be summarized in units of kilograms with descriptive statistics (both observed values and changes from baseline [Day 1]) at each visit by treatment group and for all subjects.

5.15.4. Vital Signs

The vital signs data, including orthostatic blood pressures and heart rate (calculated as standing value minus supine value), will be summarized with descriptive statistics at each visit by

treatment group and for all subjects. Both observed values and changes from baseline (Day 1) will be summarized.

Sponsor-defined PCS values for systolic blood pressure, diastolic blood pressure, and heart rate will be summarized by treatment group and for all subjects. The number and percentage of subjects with one or more PCS values at any time after Day 1 will be summarized. Note that data collected at both scheduled and unscheduled study visits will be included in this assessment. The criteria for identifying PCS values are provided in Table 4.

Table 4: Potentially Clinically Significant Criteria for Selected Vital Signs

Variable Name	PCS – Low if:			PCS – High if:		
	Observed Value is:	AND	Decrease from Baseline is:	Observed Value is:	AND	Increase from Baseline is:
Systolic Blood Pressure	<90 mmHg		≥20 mmHg	>180 mmHg		≥20 mmHg
Diastolic Blood Pressure	<50 mmHg		≥10 mmHg	>105 mmHg		≥15 mmHg
Heart Rate	<50 bpm		≥15 bpm	>120 bpm		≥15 bpm

Note that both supine and standing values of blood pressures and heart rate will be included in the identification and summary of PCS values.

A listing of all subjects with a PCS value will be presented in the study report. This listing will include vital signs data at all study visits for each subject with one or more PCS values. The listing will include subject, treatment group, visit, study day of visit, systolic blood pressure (supine and standing), diastolic blood pressure (supine and standing), and heart rate (supine and standing). Values that meet the PCS criteria will be flagged with an asterisk in the listing.

5.15.5. Electrocardiogram

The triplicate values of the quantitative ECG variables (heart rate, PR interval, QRS duration, QT interval, and Fridericia's correction of QT interval [QTcF]) measured at each visit will be averaged for the purpose of analysis. For the overall assessment categorical variable (the investigator's assessment of the ECG as Normal, Abnormal not Clinically Significant, or Abnormal Clinically Significant), which is also reported in triplicate, the value that represents the greatest degree of abnormality will be used in all summary tables.

The ECG variables will be summarized with descriptive statistics (frequency tables for the overall assessment categorical variable) by treatment group and for all subjects at each visit. Both observed values and changes from baseline (Day 1) will be summarized (for the overall categorical assessment, only observed values will be summarized).

Categorical summaries will be presented also for the QT and QTcF interval data. For these summaries, a subject's highest reported postbaseline value (including assessments at both scheduled and unscheduled study visits) will be used to determine in which category(s) the subject will be counted.

Two categorical summaries will be presented for the QT and QTcF intervals (each interval will be summarized separately). For the first summary, the number and percentage of subjects in each treatment group (and for all subjects) whose highest reported QT/QTcF value after Day 1 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 in each treatment group (and for all subjects) whose largest QT/QTcF increase from their baseline value meets the following thresholds:

- Greater than 30 msec
- Greater than 60 msec

5.15.6. Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS data will be presented in the following summaries:

- Screening/baseline lifetime assessment by treatment group and for all subjects
- Screening/baseline past 3 months assessment by treatment group and for all subjects
- Valbenazine treatment period assessments (after Day 1 through final visit) by treatment group and for all subjects

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

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

For the valbenazine treatment period, the C-SSRS responses for all assessments for a subject (including both scheduled and unscheduled visits) 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 (Day 1) scores will be presented using the "past 3 months" assessment scores as baseline. 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 for each treatment group and for all subjects, with the rows representing the baseline score and the columns representing the maximum score recorded during the valbenazine treatment period (across all visits, including unscheduled visits). Subjects missing either a baseline score or all postbaseline scores will not be included in the shift tables.

A summary listing of individual subject data will be presented for the C-SSRS data and will be provided in the study report. This summary will list subjects with a positive response for suicidal ideation, suicidal behavior, or self-injurious behavior without suicidal intent at any time after Day 1. The listing will be in the form of a table, with each row representing a subject visit (including treatment group and study day for that visit), and a column for each suicidal ideation item (1 – 5), each suicidal behavior item (6 – 10), and a final column for self-injurious behavior without suicidal intent. The cells of the table will be populated with "Y" or "N," representing either a positive or negative response, respectively, for each item in the table (ie, for each column of the table).

5.15.7. Prior and Concomitant Medications

The number and percentage of subjects using prior medications (taken within the 30 days prior to Day 1) and concomitant medications (taken during the study) classified 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 name will be summarized by treatment group and for all subjects for each study period as described in the next paragraph. 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.

Medications will be assigned to one or both of two study periods (prestudy period vs. valbenazine treatment period) based on the medication start and stop dates relative to the first dose of study drug. For example, medications that were started and stopped prior to the date of the first dose of study drug will be assigned to the prestudy period only, while medications

started prior to the first dose of study drug and either stopped during the valbenazine treatment period or indicated as "ongoing" will be assigned to both the prestudy period and the valbenazine treatment period.

5.16. Additional Data Presentations

5.16.1. Patient Satisfaction Questionnaire

Each of the five patient satisfaction questionnaire (PSQ) response categories will be assigned a numerical score as follows:

- Very satisfied = 1
- Somewhat satisfied = 2
- Neither satisfied nor dissatisfied = 3
- Somewhat dissatisfied = 4
- Very dissatisfied = 5

5.16.1.1. Patient Satisfaction Questionnaire Descriptive Statistics

Descriptive statistics (including both categorical variable statistics [using response categories] and continuous variable descriptive statistics [using numerical scores]) will be presented by treatment group and overall for the PSQ data at each visit.

Descriptive statistics for PSQ scores and response categories will be presented also by disease category subgroup (schizophrenia/schizoaffective disorder or mood disorder).

Changes from baseline (Day 1) at each postbaseline visit will be included in the summaries of PSQ numerical scores.

5.16.1.2. Patient Satisfaction Questionnaire Responder Analysis

A subject will be classified as a PSQ responder at a given visit if their score is equal to a "1" or a "2". The number and percentage of subjects classified as responders at each visit (including the baseline visit) will be summarized by treatment group. This summary will also be presented by disease category subgroup.

5.16.1.3. Patient Satisfaction Questionnaire Graphs

Mean (±SEM) values of the PSQ scores and changes from baseline at each visit will be summarized in line graphs by treatment group. Bar graphs of the percentage of subjects who are PSQ responders will also be presented for each treatment group at each visit.

5.16.2. Social Functioning Scale (SFS)

The SFS data will be presented in a data listing by subject.

5.16.3. Inclusion and Exclusion Criteria

Inclusion and exclusion criteria deviations results will be presented in a data listing by subject.

5.16.4. Pregnancy Test Results

Serum and urine pregnancy test results will be presented in a listing by subject.

5.16.5. Urine Drug Screen and Alcohol Breath Test

Urine drug screen and alcohol breath test results will be presented in a listing by subject.

6. DEVIATIONS FROM PROTOCOL PLANNED ANALYSIS

The SAP includes a number of additional summaries not described in the study protocol. In addition, the summary of study drug dosing and compliance will not include a summary of the estimated number of doses taken.

7. PERFORMANCE QUALIFICATION OF

The analysis and summary of data from this study will be performed using . All 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 log files. In addition, tables, figures, listings, and statistical analysis output will be independently reviewed for completeness and accuracy.

8. REFERENCES

None.