CLINICAL STUDY PROTOCOL

Amendment No. 2 Final Version Date: 14 May 2019

Amendment No. 1 Final Version Date: 13 September 2018

Original Final Version Date: 18 July 2018

A Phase 4, Double-Blind, Placebo-Controlled, Randomized Withdrawal Study to Evaluate the Persistence of Effect and Safety of Valbenazine for the Treatment of Tardive Dyskinesia

Study No.: NBI-98854-TD4002

Development Phase: Phase 4

Sponsor: Neurocrine Biosciences, Inc.
12780 El Camino Real
San Diego, CA 92130
Telephone: (858) 617-7600
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SIGNATURES:

I agree to conduct this study in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- Established principles of International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practices (GCP)
- United States (US) Code of Federal Regulations (CFR); US Food and Drug Administration (FDA)

CLINICAL STUDY TITLE:

A Phase 4, Double-Blind, Placebo-Controlled, Randomized Withdrawal Study to Evaluate the Persistence of Effect and Safety of Valbenazine for the Treatment of Tardive Dyskinesia

PROTOCOL No.: NBI-98854-TD4002

As Agreed:

_____ _____

Principal Investigator Signature Date

PRINCIPAL INVESTIGATOR:

_____

(Print Principal Investigator Name)

SITE:

_____

(Print Site Name)

Accepted for the Sponsor:

SPONSOR: Neurocrine Biosciences, Inc.
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Date [redacted]

LIST OF CENTRAL LABORATORIES

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2. SYNOPSIS

Protocol Title: A Phase 4, Double-Blind, Placebo-Controlled, Randomized Withdrawal Study to Evaluate the Persistence of Effect and Safety of Valbenazine for the Treatment of Tardive Dyskinesia

Study Site(s): Approximately 50 study sites in North America.

Objectives:

Primary:

- To evaluate the persistence of effect of valbenazine in subjects with tardive dyskinesia (TD) who receive placebo in a double-blind, randomized withdrawal period following open-label treatment with valbenazine.

Secondary:

- To evaluate the relationship between subject clinical characteristics and persistence of effect of valbenazine during the double-blind, placebo-controlled treatment period.
- To evaluate the effect of valbenazine on measures of quality of life and disability when administered once daily for up to 16 weeks.
- To evaluate the safety and tolerability of valbenazine administered once daily for up to 16 weeks.

Study Design: This is a Phase 4, randomized, double-blind, placebo-controlled study to evaluate the persistence of effect of valbenazine 40 mg and 80 mg. Approximately 120 medically stable male and female subjects with clinical diagnoses of schizophrenia or schizoaffective disorder with neuroleptic-induced TD or mood disorder with neuroleptic-induced TD will be enrolled.

The study includes an initial open-label treatment period for 8 weeks, followed by a double-blind, placebo-controlled treatment period for 8 weeks, for a total of up to 16 weeks of treatment. A final study visit will be conducted at Week 20 or upon early termination.

Before subjects can provide informed consent, the investigator (or designee) must determine whether the subject has the capacity to provide consent for study participation using the University of California, San Diego Brief Assessment of Capacity to Consent (UBACC). Only subjects who are deemed to have the capacity to provide consent may sign the informed consent form (ICF). All subjects must sign an ICF prior to the conduct of any study-related procedures. Subjects will be screened for eligibility for up to 6 weeks prior to Day 1 (baseline visit).

Eligible subjects will be enrolled in the study on Day 1. Valbenazine will be self-administered (in the presence of the subject's caregiver, if applicable) beginning on Day 1; the subject will be directed to take their dose at about the same time each day. During the open-label treatment period, subjects will receive 40 mg for the first week followed by 80 mg for 7 weeks.

At the end of Week 8, subjects will be randomized 1:1 to valbenazine or placebo. Subjects randomized to valbenazine will continue with the same dose as the last dose they received during the open-label treatment period. Randomization will be stratified based on the use of concomitant antipsychotic medication; this will include up to 40 subjects who are not using antipsychotic medications (ie, have not used antipsychotic medication for at least 60 days prior to screening and have no plans for resuming antipsychotic treatment during the course of the study) and the remaining subjects will be using concomitant antipsychotic medications.

At any time during treatment (open-label and placebo-controlled treatment periods), subjects who are unable to tolerate the 80 mg dose will have their dose decreased to 40 mg (during the double-blind, placebo-controlled treatment period, this will be done in a blinded manner; subjects receiving placebo will continue to receive placebo). Subjects who are unable to tolerate the 40 mg dose will be discontinued from the study.

Persistence of effect, safety, health-related quality of life, disability, and pharmacokinetics (PK) will be assessed at scheduled times throughout the study. Visits during the open-label treatment period, the double-blind, placebo-controlled treatment period, and the final study visit will have windows of ±6 days.

Study Population: Approximately 120 medically stable male and female subjects with clinical diagnoses of schizophrenia or schizoaffective disorder with neuroleptic-induced TD or mood disorder with neuroleptic-induced TD will be enrolled. The subjects must be 18 to 85 years of age (inclusive) and have moderate or severe TD as assessed by an External Abnormal Involuntary Movement Scale (AIMS) Reviewer, based on the subject's AIMS video recording conducted at screening. Subjects must be psychiatrically stable as determined clinically by the investigator (or designee), including a Brief Psychiatric Rating Scale (BPRS) score of <50 at screening.

Duration of Treatment and Study Participation: The expected duration of study participation for each subject is approximately 26 weeks, including up to 6 weeks of screening, 16 weeks of treatment, and a final study visit 4 weeks after the last dose of study drug.

Investigational Product, Dosage and Mode of Administration: Valbenazine will be supplied as capsules containing 20 and 40 mg of valbenazine (free base equivalent). The doses that will be used in this study are: 40 mg (taken as two 20 mg capsules) and 80 mg (taken as two 40 mg capsules). Subjects will swallow the capsules with at least 250 mL of water. Study drug may be taken with or without food and should be taken at about the same time each day.

Reference Therapy, Dose and Mode of Administration: Matching placebo capsules identical in appearance will be taken orally once daily with at least 250 mL of water. Study drug may be taken with or without food and should be taken at about the same time each day.

Criteria for Evaluation:

Persistence of effect:

Persistence of effect after randomization to either placebo or valbenazine will be determined based on the AIMS, adverse events (AEs) of TD, and discontinuation from the study due to lack of efficacy during the double-blind, placebo-controlled treatment period. Persistence of effect after randomization to either placebo or valbenazine will be based primarily on the mean changes from the randomization visit (end of Week 8) in the AIMS dyskinesia total score to each visit during the double-blind, placebo-controlled treatment period.

The AIMS will be administered by the investigator (or designee) at screening, on Day 1, end of Weeks 8, 12, 16, and at the final study visit (end of Week 20 or early termination). Each AIMS administration will be video recorded following standardized guidelines. An External AIMS Reviewer will evaluate the subject's global severity of TD at screening to determine eligibility. Blinded, Central

AIMS Video Raters will score AIMS Items 1 through 7 of the AIMS video recordings from Day 1, end of Weeks 8, 12, 16, and the final study visit (end of Week 20 or early termination).

Health-related quality life and disability:

The EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) (to assess health-related quality of life) and the Sheehan Disability Scale (SDS) (to assess disability) will be completed by the subject on Day 1, at Weeks 8 and 16, and at the final study visit (end of Week 20 or early termination).

Plasma drug exposure:

Blood samples to evaluate plasma concentrations of valbenazine and the active metabolite NBI-98782 (other metabolites may be evaluated) will be collected on Day 1, and at the end of Weeks 8, 12, and 16.

Safety:

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

All subjects:

- AEs
- Clinical laboratory tests (hematology, clinical chemistry, and urinalysis)
- Vital signs (including orthostatic blood pressures and pulse)
- Physical examinations
- 12-lead electrocardiograms (ECGs)
- Suicidal ideation and behavior – evaluated using the Columbia-Suicide Severity Rating Scale (C-SSRS)
- BPRS

Statistical Methods: Descriptive statistics, including confidence intervals, will be used to evaluate the persistence of effect of valbenazine during the double-blind, placebo-controlled treatment period. The primary measure of persistence of effect is the mean change from the end of the open-label treatment period (Week 8) in the AIMS dyskinesia total score (based on AIMS scores provided by blinded, Central AIMS Video Raters) in subjects who receive placebo during the double-blind, placebo-controlled treatment period. The relationship between subject clinical characteristics (including psychiatric diagnosis, age, gender, concomitant use of antipsychotic medications, and other parameters) and the persistence of effect of valbenazine during the double-blind, placebo-controlled treatment period will be evaluated using descriptive statistics and graphical methods. Safety, PK, health-related quality of life, and disability data will be summarized with descriptive statistics.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

3. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
$AUC_{0-\infty}$	area under the plasma concentration versus time curve from 0 hours extrapolated to infinity
β-hCG	β-human chorionic gonadotropin
BMI	body mass index
BPRS	Brief Psychiatric Rating Scale
CFR	Code of Federal Regulations
C_{max}	maximum plasma concentration
CRF	case report form
CRT	controlled room temperature
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSPV	Drug Safety and Pharmacovigilance
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EDTA K_2	dipotassium ethylenediaminetetraacetic acid
EPSE	extrapyramidal side effects
EQ-5D-5L	EuroQol 5 Dimensions 5 Levels
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GGT	gamma-glutamyl transferase
HBsAg	hepatitis B surface antigen
HCV-Ab	hepatitis C virus antibody
HIV-Ab	human immunodeficiency virus antibody
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IRB	Institutional Review Board
IRB/EC	Institutional Review Board/Ethics Committee
MedDRA	Medical Dictionary for Regulatory Activities
NBI	Neurocrine Biosciences, Inc.
OTC	over-the-counter
PK	pharmacokinetic(s)
prn	as needed
QTcF	corrected QT interval using Fridericia's formula
SAE	serious adverse event

SAP	Statistical Analysis Plan
SDS	Sheehan Disability Scale
$t_{½}$	terminal half-life
TD	tardive dyskinesia
TEAE	treatment-emergent adverse event
t_{max}	time to maximum plasma concentration
TS	Tourette syndrome
UBACC	University of California, San Diego Brief Assessment of Capacity to Consent
UDS	urine drug screen
ULN	upper limit of normal
US	United States
VMAT2	vesicular monoamine transporter 2
WBC	white blood cell

4. ETHICS

The study will be conducted in accordance with Neurocrine Biosciences, Inc. (NBI) standards that meet regulations relating to Good Clinical Practice (GCP). These standards respect the following guidelines:

- Good Clinical Practice: Consolidated Guideline (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH; current version]).
- United States (US) Code of Federal Regulations (CFR) dealing with clinical studies (21 CFR parts 50, 54, 56, 312, and 314).

The ethical requirements of Institutional Review Boards/Ethics Committees (IRBs/ECs) and the informed consent forms (ICFs) are discussed in Section 14.

5. INTRODUCTION

5.1. Background

Valbenazine (valbenazine tosylate, NBI-98854) is a selective, orally active vesicular monoamine transporter 2 (VMAT2) inhibitor developed by NBI. Valbenazine was approved by the US Food and Drug Administration (FDA) in April 2017 for the treatment of adults with tardive dyskinesia (TD), under the trade name INGREZZA®. Valbenazine is also under development for the treatment of Tourette syndrome (TS).

TD is a neurological condition characterized by involuntary movements of the orofacial region (ie, tongue, lips, jaw, face), the extremities, and trunk. While isolated case reports of TD after short-term exposure exist, most often TD develops after long-term neuroleptic drug use and often persists after discontinuation of such medications. The Diagnostic and Statistical Manual of Mental Disorders (DSM) Fifth Edition defines chronic exposure to neuroleptics as a criterion for TD diagnosis. In addition to duration and amount of neuroleptic exposure, other risk factors for TD appear to include older age, schizophrenia, and cognitive impairment (Margolese et al., 2005). TD can be disabling, lead to bodily harm (eg, lip or tongue lacerations, falls), interfere with activities of daily living, and result in social isolation.

5.2. Valbenazine (NBI-98854)

In nonclinical studies, valbenazine appears to cause little or no cytochrome P450 (CYP) enzyme inhibition or induction at pharmacologically relevant concentrations. Valbenazine is a moderate inhibitor of P-glycoprotein (P-gp), but only at concentrations that could be achieved in the gastrointestinal (GI) tract and is not an inhibitor of a panel of other drug transporters. Metabolism of valbenazine is characterized by hydrolysis of valbenazine to NBI-98782, and CYP3A4/5-dependent mono-oxidation to NBI-136110. NBI-98782 is metabolized in part by CYP2D6. All 3 entities, namely, valbenazine, NBI-98782, and NBI-136110, have the ability to bind to and inhibit VMAT2. However, NBI-98782 is the most potent and appears to be responsible for the majority of the observed pharmacological activity of VMAT2 inhibition.

Phase 1 clinical studies with valbenazine have been conducted in healthy subjects (including drug-drug interaction studies conducted with digoxin, ketoconazole, midazolam, and rifampin),

in hepatically impaired subjects, and in children and adolescents with TS. Phase 2 and 3 studies have been conducted in subjects with TD and a clinical diagnosis of schizophrenia or schizoaffective disorder or mood disorder. Over 850 subjects have been exposed to valbenazine in clinical studies.

Valbenazine appears to be rapidly absorbed with a time to maximum plasma concentration (t_{max}) typically ranging from approximately 0.5 to 1.0 hours. Valbenazine reaches steady state within 1 week. The active metabolite NBI-98782 gradually forms with a t_{max} of 4 to 8 hours and both valbenazine and NBI-98782 are eliminated with a terminal half-life ($t_{½}$) of 15 to 22 hours. Coadministration of ketoconazole (strong CYP3A4/5 inhibitor) with valbenazine led to a 1.5- and 1.6-fold increase in the maximum plasma concentration (C_{max}) of valbenazine and NBI-98782, respectively, and a 2.1-fold increase in the area under the plasma concentration versus time curve (AUC) from 0 hours extrapolated to infinity ($AUC_{0-\infty}$) of valbenazine and NBI-98782. Coadministration of valbenazine and rifampin (strong CYP3A4/5 inducer) led to an approximate 30% and 70% decrease in C_{max} and $AUC_{0-\infty}$, respectively, for valbenazine, and an approximate 50% and 80% decrease, respectively, for NBI-98782 compared with administration of valbenazine alone. Coadministration of valbenazine 80 mg and 0.5 mg digoxin resulted in an approximate 1.9-fold increase in the C_{max} of digoxin. The effect of valbenazine on digoxin $AUC_{0-\infty}$ was modest (1.4-fold increase) and the mean $t_{½}$ of digoxin was similar with and without valbenazine administration. Midazolam C_{max} and $AUC_{0-\infty}$ were similar with and without valbenazine administration.

Results from the completed 6-week, placebo-controlled treatment period in the TD Phase 3 study (NBI-98854-1304) indicated a statistically significant improvement in the Abnormal Involuntary Movement Scale (AIMS) dyskinesia total score mean change from baseline for valbenazine 80 mg compared with placebo.

Valbenazine has been generally well tolerated in single doses up to 300 mg and in multiple doses of up to 100 mg. During the TD 6-week, placebo-controlled period in 3 Phase 2 and 3 studies (NBI-98854-1201, -1202, and -1304), adverse reactions reported ≥3% and >placebo were somnolence (somnolence, fatigue, and sedation; 10.9% valbenazine vs 4.2% placebo), anticholinergic effects (dry mouth, constipation, disturbance in attention, vision blurred, and urinary retention; 5.4% vs 4.9%), balance disorders/fall (fall, gait disturbance, dizziness, balance disorder; 4.1% vs 2.2%), and headache (3.4% vs 2.7%). Other adverse reactions observed during premarketing evaluation of valbenazine (≥1% and >placebo), including long-term studies with up to 48 weeks of treatment, were blood glucose increased, weight increased, respiratory infections, drooling, dyskinesia, extrapyramidal symptoms (non-akathisia), anxiety, and insomnia. Overall, the incidence of adverse events (AEs) leading to discontinuation during the TD 6-week, placebo-controlled period in 3 Phase 2 and 3 studies was similar between NBI-98854-treated subjects (10 subjects, 4%) compared to those who received placebo (8 subjects, 5%).

Serious adverse events (SAEs) reported in >2 subjects across the clinical development program included schizophrenia (7 subjects); suicidal ideation (6 subjects); and schizoaffective disorder, abdominal pain, mental status change, syncope, and chronic obstructive pulmonary disease (3 subjects each). SAEs considered possibly related to study drug were reported in 4 subjects: hepatitis acute, suicidal ideation, confusional state, and hypersensitivity; all in subjects taking valbenazine. Valbenazine does not appear to increase suicidality. Valbenazine may prolong the

QT interval, although the degree of QT prolongation is not clinically significant at concentrations expected with recommended dosing (40 and 80 mg). A dose-related increase in prolactin, alkaline phosphatase and bilirubin was observed in controlled studies.

5.3. Study and Dose Rationale

The commercial starting dose of valbenazine 40 mg once daily was selected for this study and increased to the recommended dose of 80 mg once daily after 1 week of treatment.

As part of the Phase 2 and 3 placebo-controlled and open-label clinical studies, TD severity was assessed after discontinuation of valbenazine. Results from these studies indicated that not all subjects have a return of TD after washout. As such, there is interest in understanding the potential factors associated with possible clinical remission.

6. STUDY OBJECTIVES

The objectives of this clinical study are as follows:

Primary:

- To evaluate the persistence of effect of valbenazine in subjects with TD who receive placebo in a double-blind, randomized withdrawal period following open-label treatment with valbenazine.

Secondary:

- To evaluate the relationship between subject clinical characteristics and persistence of effect of valbenazine during the double-blind, placebo-controlled treatment period.
- To evaluate the effect of valbenazine on measures of quality of life and disability when administered once daily for up to 16 weeks.
- To evaluate the safety and tolerability of valbenazine administered once daily for up to 16 weeks.

7. STUDY DESIGN

This is a Phase 4, randomized, double-blind, placebo-controlled study to evaluate the persistence of effect of valbenazine 40 mg and 80 mg. Approximately 120 medically stable male and female subjects with clinical diagnoses of schizophrenia or schizoaffective disorder with neuroleptic-induced TD or mood disorder with neuroleptic-induced TD will be enrolled.

The study includes an initial open-label treatment period for 8 weeks, followed by a double-blind, placebo-controlled treatment period for 8 weeks, for a total of up to 16 weeks of treatment. A final study visit will be conducted at Week 20 or upon early termination.

Before subjects can provide informed consent, the investigator (or designee) must determine whether the subject has the capacity to provide consent for study participation using the University of California, San Diego Brief Assessment of Capacity to Consent (UBACC; Jeste et al., 2007). Only subjects who are deemed to have the capacity to provide consent may

sign the ICF. All subjects must sign an ICF prior to the conduct of any study-related procedures. Subjects will be screened for eligibility for up to 6 weeks prior to Day 1 (baseline visit).

Eligible subjects will be enrolled in the study on Day 1. Valbenazine will be self-administered (in the presence of the subject's caregiver, if applicable) beginning on Day 1; the subject will be directed to take their dose at about the same time each day. During the open-label treatment period, subjects will receive 40 mg for the first week followed by 80 mg for 7 weeks.

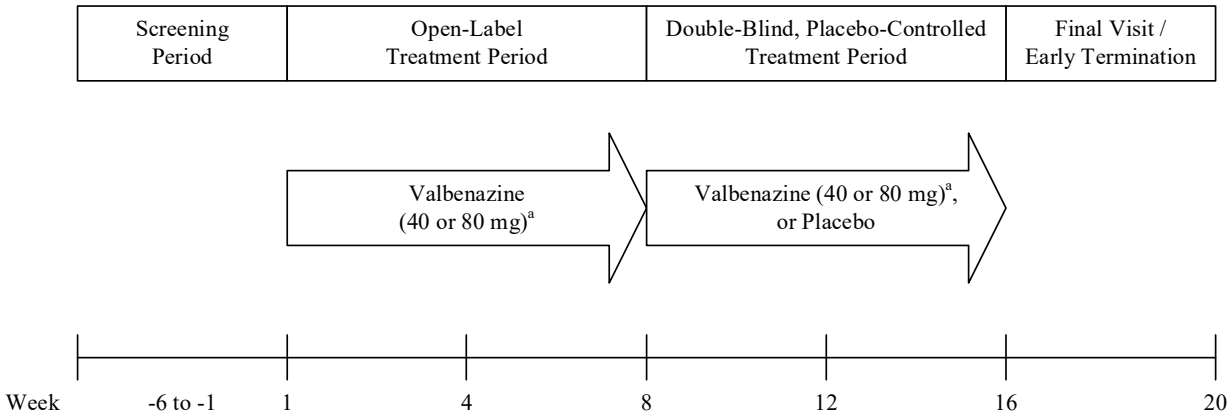
At the end of Week 8, subjects will be randomized 1:1 to valbenazine or placebo. Subjects randomized to valbenazine will continue with the same dose as the last dose they received during the open-label treatment period. Randomization will be stratified based on the use of concomitant antipsychotic medication; this will include up to 40 subjects who are not using antipsychotic medications (ie, have not used antipsychotic medication for at least 60 days prior to screening and have no plans for resuming antipsychotic treatment during the course of the study) and the remaining subjects will be using concomitant antipsychotic medications.

At any time during treatment (open-label and placebo-controlled treatment periods), subjects who are unable to tolerate the 80 mg dose will have their dose decreased to 40 mg (during the double-blind, placebo-controlled treatment period, this will be done in a blinded manner; subjects receiving placebo will continue to receive placebo). Subjects who are unable to tolerate the 40 mg dose will be discontinued from the study.

Persistence of effect, safety, health-related quality of life, disability, and pharmacokinetics (PK) will be assessed at scheduled times throughout the study. Visits during the open-label treatment period, the double-blind placebo-controlled treatment period, and the final study visit will have windows of ±6 days.

The study design schematic is provided in Figure 1.

Figure 1: Study Design Schematic



[a] During the open-label treatment period, subjects will receive 40 mg for the first week followed by 80 mg for 7 weeks. At any time during treatment, subjects who are unable to tolerate the 80 mg dose will have their dose decreased to 40 mg. Subjects randomized to valbenazine will continue with the same dose as the last dose they received during the open-label treatment period.

8. STUDY POPULATION

Approximately 120 medically stable male and female subjects with clinical diagnoses of schizophrenia or schizoaffective disorder with neuroleptic-induced TD or mood disorder with neuroleptic-induced TD will be enrolled. The subjects must be 18 to 85 years of age (inclusive) and have moderate or severe TD as assessed by an External AIMS Reviewer, based on the subject's AIMS video recording conducted at screening. Subjects must be psychiatrically stable as determined clinically by the investigator (or designee), including a Brief Psychiatric Rating Scale (BPRS) score of <50 at screening.

8.1. Inclusion Criteria

To participate in this study, subjects must meet the following criteria:

1. Be male or female aged 18 to 85 years (inclusive).
2. Subjects of childbearing potential must agree to use contraception consistently from screening until 30 days (females) or 90 days (males) after the last dose of the study drug. A female subject of childbearing potential includes those who are not surgically sterile (ie, bilateral oophorectomy, hysterectomy or bilateral tubal ligation for at least 3 months prior to screening) and those who have not been postmenopausal for at least 1 year. A male subject of childbearing potential is defined as a subject who has not been vasectomized for at least 3 months prior to screening.

   Acceptable methods of contraception include the following:

   - Condom with spermicide (cream, spray, foam, gel, suppository, or polymer film).
   - Diaphragm with spermicide (with or without condom).
   - Cervical cap with spermicide (with or without condom).
   - Vaginal sponge impregnated with spermicide used with a condom.

- Intrauterine device (IUD).
- Hormonal contraception taken for at least 3 months prior to screening.

The following subjects are not required to use contraception:

- Subjects who practice total abstinence from sexual intercourse as the preferred lifestyle (periodic abstinence is not acceptable).
- Female subjects with male partners not of childbearing potential or male subjects not of childbearing potential.
- Female subjects not of childbearing potential.

3. Female subjects of childbearing potential must have a negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test at screening and a negative urine pregnancy test on Day 1.
4. Have one of the following clinical diagnoses for at least 3 months prior to screening:
   - Schizophrenia or schizoaffective disorder as defined in the DSM (eg, DSM-IV or -5).
   - Mood disorder as defined in the DSM (eg, DSM-IV or -5).

   This criterion will be satisfied if the subject is able to provide a medical record of the diagnosis or reliable self-reported medical history and medications taken for the disorder. If the subject is unable to provide a medical record or reliable self-reported medical record, the investigator must confirm the psychiatric diagnosis based on an evaluation using the Mini International Neuropsychiatric Interview (MINI) (applicable module must be used to assess underlying disease).
5. Have a clinical diagnosis of neuroleptic-induced TD as defined in the DSM (eg, DSM-IV or -5) for at least 3 months prior to screening. This criterion will be satisfied if the subject is able to provide a medical record of the TD diagnosis or the investigator can confirm the TD diagnosis based on physical examination, and reliable self-reported medical history and medication use that show evidence of involuntary movements associated with dopamine antagonist/antipsychotic medication exposure that are clearly distinct from the parkinsonism associated with extrapyramidal symptoms or extrapyramidal side effects (EPSE).
6. Have moderate or severe TD as assessed by an External AIMS Reviewer using a video recording of the subject's AIMS assessment administered at the clinical site by the investigator (or designee) at screening.
7. Maintenance medication(s) for schizophrenia or schizoaffective disorder, mood disorders, and other protocol-allowed concurrent medications should be at a stable dose (including no changes to the dose and frequency of ongoing medications and no discontinuation of medications for a minimum of 30 days before Day 1). Benzodiazepines must be at a stable dose for 2 weeks before Day 1. This criterion will be satisfied if the investigator can confirm prior and current medications and doses through reliable subject-reported information (eg, subject provides a list of medications and doses).
8. Subjects (including those with a diagnosis of schizophrenia or schizoaffective disorder who are not using antipsychotic medication) must have a stable psychiatric status as clinically determined by the investigator. Subjects with a diagnosis of bipolar disorder must be on

stable dose of mood stabilizer(s) (eg, lithium, valproate, olanzapine) for a minimum of 30 days before Day 1.

9. Be in good general health and expected to complete the clinical study as designed.
10. Have a body mass index (BMI) of 18 to 42 kg/m^2 (inclusive) at screening (BMI is defined as the subject's weight in kg divided by the square of the subject's height in meters).
11. Have adequate hearing, vision, and language skills to perform the procedures specified in the protocol.
12. Have voluntarily provided informed consent and have signed an ICF indicating that the purpose of the study has been explained, and are willing and able to adhere to the study regimen and study procedures described in the ICF. Subjects must also have been deemed capable of providing consent to study participation using the UBACC prior to signing the ICF.
13. Have a negative urine drug screen (UDS) (for amphetamines, barbiturates, benzodiazepines, phencyclidine, cocaine, methamphetamine, methadone, tricyclic antidepressants, and opiates) at screening (central laboratory results) and Day 1 (UDS kit results conducted at the study center), except for any subject receiving a stable dose of benzodiazepines, tricyclic antidepressants, or opiates. Subjects with positive cannabinoid results may be allowed to participate in the study provided that the subject is given thorough counseling and agrees to refrain from using cannabinoids for the duration of his/her study participation.
14. Have a negative alcohol breath test at screening and Day 1.
15. Be willing to provide authorization for access to personal health information in conjunction with US Health Insurance Portability and Accountability Act (HIPAA).

8.2. Exclusion Criteria

8.2.1. Exclusion Criteria for All Subjects

Subjects will be excluded from the study if they:

1. Have an active, clinically significant unstable medical condition within 1 month (30 days) prior to Day 1.
2. Have comorbid abnormal involuntary movement(s) (eg, parkinsonism, akathisia) that is more prominent than TD as assessed by an External AIMS Reviewer using a video recording of the subject's AIMS administration at screening.
3. Have a known history of substance dependence, or substance (drug) or alcohol abuse within the 3 months prior to Day 1 (nicotine and caffeine dependence are not exclusionary), as defined in the DSM (eg, DSM-IV).
4. Have BPRS total score of ≥50 at screening.
5. Have a significant risk of suicidal or violent behavior. Subjects with any suicidal behavior within 3 months prior to screening will be excluded. In addition, subjects with suicidal ideation of type 4 (active suicidal ideation with some intent to act, without specific plan) or type 5 (active suicidal ideation with specific plan and intent) based on the Columbia-Suicide

Severity Rating Scale (C-SSRS) in the 3 months prior to screening (using Baseline/Screening version) or Day 1 (using Since Last Visit version) will also be excluded.

6. Have been hospitalized for psychiatric disorder within 6 months prior to Day 1.
7. Have a known history of neuroleptic malignant syndrome.
8. Have a known history of long QT syndrome or cardiac arrhythmia.
9. Have a screening or Day 1 average triplicate electrocardiogram (ECG) corrected QT interval using Fridericia's formula (QTcF) of >450 msec (males) or >470 msec (females) or the presence of any clinically significant cardiac abnormality.
10. Receive any prohibited medication (see Section 9.9.3).
11. Have any of the following laboratory test abnormalities at screening:
    - Serum creatinine >1.5 times the upper limit of normal (ULN).
    - Aspartate aminotransferase (AST) ≥2.5 times ULN.
    - Alanine aminotransferase (ALT) ≥2.5 times ULN.
    - Gamma-glutamyl transferase (GGT) ≥3.0 times ULN.
    - Total bilirubin >1.5 mg/dL. Subjects with a documented diagnosis of Gilbert's syndrome are not required to meet the bilirubin criteria.
12. Have a hematologic malignancy or solid tumor diagnosed within 3 years prior to Day 1, with the exception of localized skin cancer or carcinoma in situ of the cervix.
13. Have any of the following hematologic abnormalities at screening:
    - Hemoglobin <10 g/dL.
    - White blood cell (WBC) count $<3.0 \times 10^3/mm^3$.
    - Platelet count $<100,000/mm^3$.
14. Have other laboratory results not within the laboratory's reference range and deemed by the investigator to be clinically significant.
15. Have a positive human immunodeficiency virus antibody (HIV-Ab) test result or hepatitis B surface antigen (HBsAg) test result at screening. Subjects with positive hepatitis C virus antibody (HCV-Ab) and confirmatory positive polymerase chain reaction (PCR) reflex test results at screening will be allowed to participate in the study provided that the subject is asymptomatic as assessed by the investigator and does not meet the liver function test abnormalities for ALT, AST, GGT, or total bilirubin in exclusion criterion #11.
16. Have received an investigational drug within 30 days or 5 half-lives (if known), whichever is longer, prior to Day 1 or plan to use an investigational drug (other than valbenazine) during the study.
17. Have a blood loss ≥550 mL or donated blood within 30 days prior to Day 1.
18. Currently receiving tetrabenazine or deutetrabenazine.
19. Have used valbenazine (INGREZZA) within 30 days of screening.

20. Have an allergy, hypersensitivity, or intolerance to VMAT2 inhibitors (eg, tetrabenazine, deutetrabenazine), or have a history of hypersensitivity to valbenazine or any component of INGREZZA.
21. Are currently pregnant or breastfeeding.

8.2.2. Exclusion Criteria for Subjects with Clinical Diagnosis of Mood Disorder

In addition to the exclusion criteria for all subjects, the following criteria must not be met for subjects with mood disorder:

22. Have had mood episodes (hypomania, mania, depressive, etc.) within 2 months prior to Day 1.
23. Have history of rapid cycling (>4 mood episodes per year) or ultra-rapid cycling (>4 mood episodes per month).

8.3. Subject Identification and Replacement

Subjects will be identified by their unique subject number and initials (first, middle, last; a hyphen may be used for subjects with no middle initial). The subject initials and subject number will be noted on electronic case report forms (eCRFs), all source documentation, laboratory documents, and ECG tracings. Subjects who discontinue from the study after the initiation of dosing may be replaced at the discretion of the Sponsor.

8.4. Randomization

Subjects will be randomized (1:1) to receive valbenazine or placebo at the end of Week 8. Subjects randomized to valbenazine will continue with the same dose as the last dose they received during the open-label treatment period. Randomization will be stratified based on the use of concomitant antipsychotic medication; this will include up to 40 subjects who are not using antipsychotic medications (ie, have not used antipsychotic medication for at least 60 days prior to screening and have no plans for resuming antipsychotic treatment during the course of the study) and the remaining subjects will be using concomitant antipsychotic medications.

9. STUDY EVALUATIONS

9.1. Schedule of Assessments

A schedule of assessments that summarizes the frequency and timing of all assessments is provided in Table 1.

No protocol-related procedures should be performed before informed consent has been obtained. Subject-related events and activities including specific instructions, procedures, concomitant medications, dispensing of study drug, and descriptions of AEs should be recorded in the appropriate source documents and eCRFs.

Table 1: Schedule of Assessments

Procedure	Screening Period	Open-Label Treatment Period			Double-blind, Placebo-Controlled Treatment Period		Final Study Visit/ET[b]
Week	-6 to -1	Day 1 Baseline	4	8	12	16	20
Visit[a]	1	2	3	4	5	6	7
UBACC/Informed consent[c]	X						
Inclusion/exclusion criteria	X	update					
Randomization				X			
Medical history	X	update					
Physical examination[d]	X	X	X	X	X	X	X
Height[d]	X						
Vital signs	X	X	X	X	X	X	X
12-lead ECG[e]	X	X	X	X	X	X	X
Pregnancy test[f]	X (s)	X (u)	X (u)	X (u)	X (u)	X(u)	X (u)
Serology (HBsAg, HCV-Ab and HIV-Ab)	X						
Clinical laboratory tests[g]	X	X	X	X	X	X	X
Urine drug screen[h]	X	X					
Alcohol breath test	X	X					
Genotype blood sample		X					
PK plasma sample[i]		X		X	X	X	
AIMS (with video recording)[j]	X	X		X	X	X	X
C-SSRS	X	X	X	X	X	X	X
BPRS	X	X	X	X	X	X	X
EQ-5D-5L		X		X		X	X
SDS		X		X		X	X
Valbenazine/placebo dosing[k]		X	X	X	X	X	
Dispense study drug		X	X	X	X		
Valbenazine/placebo accountability[l]			X	X	X	X	
AE monitoring	X	X	X	X	X	X	X
Prior and concomitant medications	X	X	X	X	X	X	X

Definitions and footnotes appear on the following page.

AE=adverse event; AIMS=Abnormal Involuntary Movement Scale; BPRS=Brief Psychiatric Rating Scale; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; EQ-5D-5L=EuroQol 5 Dimensions 5 Levels; ET=early termination; HBsAg=hepatitis B surface antigen; HCV-Ab=hepatitis C antibody; HIV-Ab=human immunodeficiency virus antibody; PK=pharmacokinetic(s); s=serum; SDS=Sheehan Disability Scale; u=urine; UBACC=University of California, San Diego Brief Assessment of Capacity to Consent.

a. All study visits, except screening, will have visit window of ±6 days.
b. Final study visit for subjects who complete the study (or early termination).
c. The UBACC will be used to determine whether the subject has the capacity to provide informed consent.
d. Physical examination will include measurement of weight and height without shoes (height will be measured at screening only).
e. A standard 12-lead ECG will be conducted in triplicate (at least 1 minute apart and within 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, PR intervals, and QRS duration based on the ECG machine readings (QTcF may need to be calculated).
f. Pregnancy tests are required for all women of childbearing potential. A serum pregnancy test will be conducted at screening. A urine pregnancy test will be conducted on Day 1 and at all subsequent visits.
g. Clinical laboratory tests include hematology, clinical chemistry, and urinalysis. All blood samples will be obtained under non-fasted conditions.
h. Urine drug screen will be analyzed at screening by the central lab. A UDS kit provided by the central lab will be used at the site to confirm eligibility on Day 1.
i. Subjects will be asked to record and provide dosing times on the days during the treatment period when blood PK samples are collected. PK sample on Day 1 must be predose.
j. The AIMS will be administered by the investigator (or designee). AIMS Items 11 to 12 will be completed by the investigator (or designee) administering the AIMS; AIMS Items 8 to 10 will be scored by the investigator (or designee) administering the AIMS. If possible, the same person should administer the AIMS for an individual subject at all timepoints. Subjects will be video recorded during the AIMS administration. An External AIMS Reviewer will evaluate the subject's global severity of TD at screening to determine eligibility. Blinded, Central AIMS Video Raters will review the AIMS video recordings on Day 1, end of Weeks 8, 12, 16, and at the final study visit (end of Week 20 or early termination) and will score AIMS Items 1 through 7.
k. Subjects will self-administer study drug in the presence of their caregiver (if applicable). The subject will be directed to take their dose at about the same time each day. Subject or caregiver will record the daily date and time of dosing on the drug packaging form provided.
l. Subjects will return all used and unused study drug, and a compliance check will be performed by counting the capsules returned at each study visit.

9.2. Screening and Baseline Assessments

9.2.1. Brief Psychiatric Rating Scale

The BPRS is a clinician-rated tool designed to assess the severity of psychopathology in patients with schizophrenia and other psychotic disorders (Overall and Gorham, 1962, 1988). The BPRS includes 18 items that address somatic concern, anxiety, emotional withdrawal, conceptual disorganization, guilt feelings, tension, mannerisms and posturing, grandiosity, depressive mood, hostility, suspiciousness, hallucinatory behaviors, motor retardation, uncooperativeness, unusual thought content, blunt affect, excitement, and disorientation.

The severity of each of the 18 items of the BPRS is rated on a scale of 1 (not present) to 7 (extremely severe) (total score range: 18 to 126). Higher scores represent greater symptom severity.

The investigator or other qualified site personnel will administer and score the scale at screening, and subjects must have a BPRS total score <50 to be eligible for study participation (see exclusion criterion #4). The investigator or other qualified site personnel will also administer and score the scale on Day 1, end of Weeks 4, 8, 12, 16, and the final study visit (end of Week 20 or early termination).

9.2.2. Genotyping

A blood sample will be collected from enrolled subjects for the analysis of CYP2D6 status (ie, normal, intermediate, poor, or ultrarapid metabolizers) on Day 1. Approximately 4 mL of blood will be collected in tubes containing dipotassium ethylenediaminetetraacetic acid (EDTA K_2). After the sample is obtained, it should be thoroughly mixed. The vials will be stoppered and labeled with the study barcode and subject number. The collection and submission of medical information will be accomplished with strict adherence to professional standards of confidentiality. Genotyping blood samples collected from subjects will be shipped to a central laboratory for analysis.

9.3. Persistence of Effect

9.3.1. Abnormal Involuntary Movement Scale

The severity of TD will be assessed using the AIMS rating scale. This scale was developed by the Psychopharmacology Research Branch of the National Institute of Mental Health (Guy, 1976). The AIMS rates a total of 10 items with 9 items rating involuntary movement from 0 (no dyskinesia) to 4 (severe dyskinesia). Items 1 through 7 include facial and oral movements (Items 1 to 4), extremity movements (Items 5 to 6), and trunk movements (Item 7). The AIMS dyskinesia total score for Items 1 to 7 ranges from 0 to 28; a higher score reflects increased severity. Items 8, 9 and 10 rate global judgments with Item 10 being rated 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 (with video recording) will be administered by the investigator (or designee) at screening, Day 1, end of Weeks 8, 12, 16, and at the final study visit (end of Week 20 or early termination).

9.3.1.1. AIMS Administrator

During the study, the AIMS will be administered at the study site by the investigator (or designee) according to the AIMS administration procedure provided by NBI or designee. AIMS Items 11 to 12 will be completed by the investigator (or designee) administering the AIMS; AIMS Items 8 to 10 will be scored by the investigator (or designee) administering the AIMS. If possible, the same person should administer the AIMS for an individual subject at all timepoints.

9.3.1.2. AIMS Video Recording and External AIMS Reviewer

Subjects will be video recorded for the duration of the AIMS administration (approximately 10 minutes) according to standardized guidelines provided by NBI (or designee). Video recordings of the AIMS administration will be uploaded to a secure, central AIMS server, managed by a core laboratory. Access to the dedicated central AIMS server will be limited and will require the user to provide a user identification and password to access the secure server and the subject's video recording. The AIMS video recording uploaded to the server will be viewed by the External AIMS Reviewer and Sponsor-designated representatives. The External AIMS Reviewer will review the video recordings to determine if the subject has moderate or severe TD at screening (see inclusion criterion #6).

9.3.1.3. Blinded, Central AIMS Video Raters

The AIMS video recording files will be reviewed and scored by blinded, Central AIMS Video Raters. A triple-blind consensus scoring will be conducted by these raters according to scoring guidelines developed by NBI. NBI (or designee) will provide the blinded, Central AIMS Video Raters a password-protected media (eg, flash drive) containing the subjects' randomized AIMS video recording files to review and score. The central raters will be blinded to the subjects' study visits and treatment assignments. Two blinded, Central AIMS Video Raters will together review each AIMS video file from beginning to end and must agree on the score (0 to 4) for AIMS Items 1 to 7. The blinded, Central AIMS Video Raters will review and score the AIMS video recordings conducted at Day 1, end of Weeks 8, 12, 16, and at the final study visit (end of Week 20 or early termination).

9.4. Health-Related Quality of Life and Disability Assessments

9.4.1. EuroQol 5 Dimensions 5 Levels

The EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) is a general, single index measure for describing and valuing health (Herdman et al., 2011). It defines health in terms of 5 dimensions: Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The subject indicates his/her health state by checking the box next to the most appropriate statement. The scores for the 5 dimensions can be combined into a 5-digit number that describes the patient's health state. Subjects also rate their overall health on a 0 to

100 hash-marked, vertical visual analogue scale (EQ-VAS). The endpoints are labeled 'The best health you can imagine' and 'The worst health you can imagine.'

The EQ-5D-5L will be administered at Day 1, end of Weeks 8, 16, and at the final visit (end of Week 20 or early termination).

9.4.2. Sheehan Disability Scale

The Sheehan Disability Scale (SDS) is a brief, validated measure of functional impairment in a number of psychiatric disorders to measure the effect of treatment on disability (Leon et al., 1997). 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 (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 will be administered at Day 1, end of Weeks 8, 16, and at the final visit (end of Week 20 or early termination).

9.5. Plasma Drug Exposure

Blood samples to evaluate plasma concentrations of valbenazine and the active metabolite NBI-98782 (other metabolites may be evaluated) will be collected on Day 1 (predose), and at the end of Weeks 8, 12, and 16.

For each sample, approximately 2 mL of blood will be collected in tubes containing EDTA K_2. The blood samples will be processed and stored according to the procedure as specified in the laboratory manual. Samples will be shipped on dry ice to the central laboratory for analysis.

9.6. Safety Assessments

Concomitant medication use and AEs will be monitored throughout the study as described in Section 9.9.1 and Section 11, respectively. The remaining safety assessments are described in the following sections.

For any abnormal safety assessment deemed clinically significant, the investigator will perform appropriate follow-up assessments (eg, repeat analysis), until the cause of the abnormality is determined and/or until the value returns to baseline (or within normal limits), or the investigator deems the abnormality to be of no clinical significance.

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

9.6.1. Physical Examination, Including Height and Weight

The complete physical examination will consist of an assessment of general appearance, skin and mucosae, head, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest/lungs, cardiovascular, abdomen, extremities, musculoskeletal, and neurological system. A complete physical examination including weight will be performed at screening, Day 1, end of Weeks 4, 8,

12, 16, and at the final visit (end of Week 20 or early termination). Height will be measured at screening only. Height and weight will be measured with subjects not wearing shoes.

9.6.2. Vital Sign Measurements

Vital signs will include orthostatic systolic and diastolic blood pressure, orthostatic pulse rate, respiratory rate (recorded only supine), and oral body temperature. Blood pressure will be measured using a calibrated automatic blood pressure cuff after the subject has been supine for at least 5 minutes and after approximately 2 minutes of standing. The automatic blood pressure cuff will also provide pulse rate measurement.

Vital sign measurements will be collected at screening, Day 1, end of Weeks 4, 8, 12, 16, and at the final visit (end of Week 20 or early termination). Vital sign measurements will be obtained before any scheduled blood sample collection.

9.6.3. Electrocardiogram

A standard 12-lead ECG will be recorded in triplicate (at least 1 minute apart and within 15 minutes) after the subject has rested supine for at least 5 minutes. The ECG parameters that will be assessed include heart rate, PR interval, QRS duration, QT interval, and QTcF (machine readings or calculated). Additionally, the occurrence of de- and re-polarization and rhythm disorders or other abnormalities will be assessed. Based on the review of these parameters, the investigator or designee will note if the ECG is Normal, Abnormal not Clinically Significant, or Abnormal Clinically Significant. If the ECG is Abnormal Clinically Significant, the investigator or designee will provide a description of the abnormality recorded on the AE eCRF.

The 12-lead ECG recordings will be conducted at screening, Day 1, end of Weeks 4, 8, 12, 16, and at the final visit (end of Week 20 or early termination).

9.6.4. Clinical Laboratory Assessments

All clinical laboratory assessments will be performed by a central laboratory. Results from samples collected at screening must be reviewed by the investigator or qualified designee before enrollment to confirm each subject's eligibility. In addition, certain laboratory assessments (alcohol breath test, UDS, and urine pregnancy test) will be performed by the study site at baseline (Day 1) to confirm subject eligibility. The central laboratory will provide instructions and supplies to the study staff before study initiation and instructions will be included in a laboratory manual. The laboratory test battery will include routine and screening laboratory tests.

The routine laboratory tests (hematology and clinical chemistry) and urinalysis will be performed under non-fasted conditions at screening, Day 1, end of Weeks 4, 8, 12, 16, and at the final visit (end of Week 20 or early termination). Laboratory samples will be collected in the following approximate amounts: 3 mL for hematology, 1 mL for clinical chemistry (includes serum pregnancy tests), 3 mL for serology, and 4 mL for genotyping. Approximate total blood sample volume per subject is 43 mL (including PK [2 mL per sample]).

The following clinical safety laboratory assays will be performed:

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

Clinical Chemistry: sodium, potassium, calcium, phosphorus, magnesium, chloride, blood urea nitrogen, bicarbonate, creatinine, uric acid, albumin, alkaline phosphatase, lactate dehydrogenase, AST, ALT, GGT, creatine kinase, total bilirubin, total cholesterol, triglycerides, total protein, and glucose.

Urinalysis: ketones, protein, glucose, leukocyte esterase, occult blood, and pH by dipstick; microscopic examination of sediment will be performed only if the results of the urinalysis dipstick evaluation are positive for nitrites, protein, leukocyte esterase, or blood.

The following additional laboratory tests will be performed:

Serology: Blood will be collected for HIV-Ab, HBsAg, and HCV-Ab testing at screening.

Urine Drug Screen and Alcohol Breath Test: The UDS will test for amphetamines, methamphetamine, barbiturates, phencyclidine, benzodiazepines, cannabinoids, cocaine, methadone, tricyclic antidepressants, and opiates. A UDS will be performed at screening by a certified central laboratory. A UDS will be conducted at the clinical site at Day 1 using a urine drug kit provided by the central laboratory and the results will be used to confirm study eligibility.

The alcohol breath test will be performed at screening and at Day 1.

Pregnancy Tests: Pregnancy tests will be performed for all female subjects of childbearing potential. A serum pregnancy test (β-hCG) will be performed at screening. A urine pregnancy test will be performed at the clinical site on Day 1 (a negative test result is required to be eligible for the study) and at the end of Weeks 4, 8, 12, 16, and at the final visit (end of Week 20 or early termination).

9.6.5. Columbia-Suicide Severity Rating Scale

The C-SSRS is a validated instrument to prospectively assess suicidal ideation and behavior (http://www.cssrs.columbia.edu). There are versions of the questionnaire designed for use at screening (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 1 or more screening questions will prompt additional questions that evaluate frequency and intensity of suicidal ideation and/or behavior. Subjects with any lifetime suicidal behavior within 3 months prior to screening will be excluded. In addition, subjects with suicidal ideation of type 4 (active suicidal ideation with some intent to act, without specific plan) or type 5 (active suicidal ideation with specific plan and intent) in the 3 months before screening or Day 1 based on the C-SSRS will also be excluded (see exclusion criterion #5).

The C-SSRS will be administered and scored by the investigator or qualified study site personnel at screening, Day 1, end of Weeks 4, 8, 12, 16, and at the final visit (end of Week 20 or early termination).

9.7. Specific Study Information

After providing informed consent (as required by the governing IRB), subjects will undergo screening procedures within 6 weeks of Day 1.

9.7.1. Screening (Weeks -6 to -1)

Informed Consent Process: The ICF will be reviewed with subjects. The UBACC will then be administered. Only subjects who are deemed to have the capacity to provide consent may sign the ICF. The ICF must be signed prior to the start of any screening procedures.

During screening, the following study evaluations and tasks will be performed at the study site:

- Administer the UBACC (only subjects who are deemed to have the capacity to provide consent may sign the ICF).
- Obtain informed consent.
- Assess inclusion/exclusion criteria.
- Collect medical history.
- Perform physical examination (including height and weight).
- Collect vital signs, including orthostatic systolic and diastolic blood pressures, orthostatic pulse rate, respiratory rate, and oral body temperature.
- Perform a 12-lead ECG in triplicate (at least 1 minute apart and within 15 minutes).
- Perform serum pregnancy test (β-hCG) for all female subjects of childbearing potential.
- Collect blood sample for serology testing (HBsAg, HCV-Ab, and HIV-Ab).
- Collect blood sample for hematology and clinical chemistry.
- Collect urine sample for urinalysis.
- Perform UDS and alcohol breath test.
- Administer the AIMS (including video recording).
- Administer the C-SSRS (Screening/Baseline version).
- Administer the BPRS.
- AE monitoring.
- Record prior and concomitant medications.

Subjects will be asked to refrain from taking prescription or over-the-counter (OTC) medications as specified in Section 9.9.

9.7.2. Treatment Period (Day 1 [baseline] to end of Week 16, including the open-label treatment period and the double-blind, placebo-controlled treatment period)

9.7.2.1. Baseline (Day 1)

The following study evaluations and procedures will be performed on Day 1:

- Update inclusion and exclusion criteria.
- Update medical history.

- Perform physical examination (including weight).
- Collect vital signs, including orthostatic systolic and diastolic blood pressures, orthostatic pulse rate, respiratory rate, and oral body temperature.
- Perform a 12-lead ECG in triplicate (at least 1 minute apart and within 15 minutes).
- Perform a urine pregnancy test (using pregnancy test kit) for all female subjects of childbearing potential.
- Collect blood sample for hematology and clinical chemistry.
- Collect urine sample for urinalysis.
- Perform UDS (using the urine drug kit to confirm eligibility).
- Perform alcohol breath test.
- Collect blood sample for genotyping (enrolled subjects only).
- Collect blood sample for PK (predose).
- Administer the AIMS (including video recording).
- Administer the C-SSRS (Since Last Visit version).
- Administer the BPRS.
- Administer the EQ-5D-5L.
- Administer the SDS.
- Dispense study drug.
- AE monitoring.
- Record concomitant medications.

9.7.2.2. End of Week 4 (±6 days)

The following study evaluations and procedures will be performed at the end of Week 4:

- Perform physical examination (including weight).
- Collect vital signs, including orthostatic systolic and diastolic blood pressures, orthostatic pulse rate, respiratory rate, and oral body temperature.
- Perform a 12-lead ECG in triplicate (at least 1 minute apart and within 15 minutes).
- Perform a urine pregnancy test (using pregnancy test kit) for all female subjects of childbearing potential.
- Collect blood sample for hematology and clinical chemistry.
- Collect urine sample for urinalysis.
- Administer the C-SSRS (Since Last Visit version).
- Administer the BPRS.
- Dispense study drug.
- Study drug accountability.
- AE monitoring.
- Record concomitant medications.

9.7.2.3. End of Week 8 (±6 days)

The following study evaluations and procedures will be performed at the end of Week 8:

- Randomization of subjects.
- Perform physical examination (including weight).
- Collect vital signs, including orthostatic systolic and diastolic blood pressures, orthostatic pulse rate, respiratory rate, and oral body temperature.
- Perform a 12-lead ECG in triplicate (at least 1 minute apart and within 15 minutes).
- Perform a urine pregnancy test (using pregnancy test kit) for all female subjects of childbearing potential.
- Collect blood sample for hematology and clinical chemistry.
- Collect urine sample for urinalysis.
- Collect blood sample for PK.
- Administer the AIMS (including video recording).
- Administer the C-SSRS (Since Last Visit version).
- Administer the BPRS.
- Administer the EQ-5D-5L.
- Administer the SDS.
- Dispense study drug.
- Study drug accountability.
- AE monitoring.
- Record concomitant medications.

9.7.2.4. End of Week 12 (±6 days)

The following study evaluations and procedures will be performed at the end of Week 12:

- Perform physical examination (including weight).
- Collect vital signs, including orthostatic systolic and diastolic blood pressures, orthostatic pulse rate, respiratory rate, and oral body temperature.
- Perform a 12-lead ECG in triplicate (at least 1 minute apart and within 15 minutes).
- Perform a urine pregnancy test (using pregnancy test kit) for all female subjects of childbearing potential.
- Collect blood sample for hematology and clinical chemistry.
- Collect urine sample for urinalysis.
- Collect blood sample for PK.
- Administer the AIMS (including video recording).
- Administer the C-SSRS (Since Last Visit version).
- Administer the BPRS.
- Dispense study drug.

- Study drug accountability.
- AE monitoring.
- Record concomitant medications.

9.7.2.5. End of Week 16 (±6 days)

The following study evaluations and procedures will be performed at the end of Week 16:

- Perform physical examination (including weight).
- Collect vital signs, including orthostatic systolic and diastolic blood pressures, orthostatic pulse rate, respiratory rate, and oral body temperature.
- Perform a 12-lead ECG in triplicate (at least 1 minute apart and within 15 minutes).
- Perform a urine pregnancy test (using pregnancy test kit) for all female subjects of childbearing potential.
- Collect blood sample for hematology and clinical chemistry.
- Collect urine sample for urinalysis.
- Collect blood sample for PK.
- Administer the AIMS (including video recording).
- Administer the C-SSRS (Since Last Visit version).
- Administer the BPRS.
- Administer the EQ-5D-5L.
- Administer the SDS.
- Study drug accountability.
- AE monitoring.
- Record concomitant medications.

9.7.3. Final Study Visit (end of Week 20 [±6 days]) or Early Termination

The following procedures will be conducted at the final study visit (the end of Week 20) or at early termination:

- Perform physical examination (including weight).
- Collect vital signs, including orthostatic systolic and diastolic blood pressures, orthostatic pulse rate, respiratory rate, and oral body temperature.
- Perform a 12-lead ECG in triplicate (at least 1 minute apart and within 15 minutes).
- Perform a urine pregnancy test (using pregnancy test kit) for all female subjects of childbearing potential.
- Collect blood sample for hematology and clinical chemistry.
- Collect urine sample for urinalysis.
- Administer the AIMS (including video recording).
- Administer the C-SSRS (Since Last Visit version).
- Administer the BPRS.

- Administer the EQ-5D-5L.
- Administer the SDS.
- AE monitoring.
- Record concomitant medications.

Instruct subjects to continue using contraception until 30 days after the last dose of study drug for females and 90 days after the last dose of study drug for males (see inclusion criterion #2).

9.8. Study Duration

The expected duration of study participation for each subject is approximately 26 weeks, including up to 6 weeks of screening, 16 total weeks of treatment, and a final study visit 4 weeks after the last dose of study drug.

9.9. Prohibitions and Restrictions

9.9.1. Prior and Concomitant Medications

All prescription and OTC medications, including dietary and herbal supplements, taken by subjects during the 30 days before screening and during the study will be entered on the Prior and Concomitant Medications eCRF. All medications taken for indications of schizophrenia/schizoaffective disorder, mood disorder, EPSE, and TD within the last 2 years will also be entered on the Prior and Concomitant Medications eCRF. Any additions, deletions, or changes in the dose of these medications will be entered on the eCRF with indication, dose, route, and dates of drug administration.

9.9.2. Medications to Treat Psychiatric and Medical Conditions

All coexistent diseases or conditions will be treated in accordance with prevailing medical practice. All medications to treat the subject's psychiatric and medical conditions should be on a stable treatment regimen (including no changes to the dose and frequency of ongoing medications and no new or discontinued medications) for a minimum of 30 days before Day 1, and are expected to remain stable during the study. Benzodiazepines must be at a stable dose for at least 2 weeks before Day 1. Investigators should document doses of current medication through medical or pharmacy records, confirmation with the subject's caregivers (if applicable), or through reliable subject-reported information (eg, provide a list of medications and doses).

9.9.3. Prohibited Medications

The following medications are prohibited from 30 days prior to screening (unless otherwise stated) until the final study visit (end of Week 20 or early termination) as described below:

- Antiemetics: Metoclopramide, prochlorperazine, and promethazine are prohibited.
- Botulinum toxin: Botulinum toxin injections are prohibited starting 90 days prior to screening and during the study.
- CYP3A4 inducers: Strong inducers of CYP3A4 (eg, phenobarbital, rifabutin, rifampin, primidone, St. John's Wort) are prohibited.

- CYP3A4 inhibitors: Strong inhibitors of CYP3A4 (eg, itraconazole, ketoconazole, clarithromycin).
- Dopamine agonists and precursors: Dopamine receptor agonists (eg, ropinirole) and precursors (eg, carbidopa/levodopa) are prohibited.
- Monoamine oxidase inhibitors (MAOIs): All MAOIs (eg, isocarboxazid, phenelzine, selegiline, tranylcypromine) are prohibited.
- Stimulants: Stimulants (eg, amphetamine, methylphenidate, ephedrine, pseudoephedrine, phenylephrine, and phenylpropanolamine) are prohibited.
- VMAT2 inhibitors: VMAT2 inhibitor medications (eg, tetrabenazine, deutetrabenazine, reserpine) are prohibited, except for valbenazine.

As needed use of the following medications is strictly prohibited: anticholinergics, benzodiazepines, opiates, antipsychotics, mood stabilizers, antidepressants, tricyclic antidepressants, strong CYP3A4 inhibitors and inducers, and strong CYP2D6 inhibitors.

9.9.4. General and Dietary Restrictions

Subjects must agree to adhere to the following prohibitions and restrictions during the study in order to be eligible to participate:

- Return to the study center at baseline (Day 1), end of Weeks 4, 8, 12, 16, and at the final visit (end of Week 20 or early termination).
- Not to use any prohibited concomitant medication.
- Subjects must limit alcohol use to less than 7 drinks per week during the course of the study.
- Not to donate blood during the study, including the screening period, and for 4 weeks after completion of the study. Male subjects must agree to refrain from donating sperm during the study and for 90 days after the last dose of the study drug.
- Not to participate in an investigational drug study for at least 30 days after the last dose of study drug or 30 days after study completion, whichever is longer.

9.10. Withdrawal Criteria

Subjects are free to discontinue their participation in the study at any time. The investigator must withdraw any subject from the study if that subject requests to be withdrawn.

The investigator must withdraw the subject from the study if the subject experiences any of the following:

- If the type, frequency, or severity of any AE becomes unacceptable/intolerable.
- If the subject is unable to tolerate the starting dose or resumption of the previous dose.
- QTcF value >500 msec (value must be verified by a cardiologist) on any ECG tracing.
- If the subject exhibits suicidal behavior, or suicidal ideation of type 4 (active suicidal ideation with some intent to act, without specific plan) or type 5 (active suicidal ideation with specific plan and intent) based on the C-SSRS.
- Is lost to follow-up.

- Subject is confirmed to be pregnant.

The investigator or NBI may withdraw the subject from the study if the subject experiences any of the following:

- Develops a clinically significant laboratory (eg, ALT or AST ≥2.5 times ULN or total bilirubin >2.0 times ULN) or ECG abnormality.
- Requires a medication that is prohibited by the protocol (refer to Section 9.9.3).

All subjects prematurely discontinuing the study, regardless of cause, should be encouraged have all early termination assessments performed, if possible (see Section 9.7.3).

9.10.1. Handling of Withdrawals

If a subject prematurely withdraws from the study, either at his/her request, or at the investigator's discretion, the investigator will record the reason for withdrawal on the relevant eCRF. All subjects who withdraw from the study prematurely should have all early termination assessments performed.

It is crucial to obtain follow-up data for any subject withdrawn because of an AE, abnormal laboratory test, vital sign measurement, physical examination, or ECG finding. In any case, every effort must be made to undertake safety follow-up procedures.

9.10.2. Sponsor's Termination of Study

NBI reserves the right to discontinue the study at any time for clinical or administrative reasons. Such a termination must be implemented by the investigator, if instructed to do so by NBI in a time frame that is compatible with the subjects' well-being.

10. STUDY DRUG

10.1. Study Drug Supplies

Valbenazine will be supplied as capsules containing 20 and 40 mg of valbenazine (free base equivalent). The doses that will be used in this study are: 40 mg (taken as two 20 mg capsules) and 80 mg (taken as two 40 mg capsules).

The matching placebo capsules are identical in appearance to the valbenazine capsules.

10.2. Study Drug Storage

Valbenazine and placebo capsules must be stored at controlled room temperature (CRT) (20˚C to 25˚C or 68˚F to 77˚F) under the conditions specified in the Investigator's Brochure and in a locked area accessible only to the pharmacist (or designee) until dispensing. Excursions outside this range will be allowed provided they meet the following conditions:

- Storage between refrigerated conditions (2˚C or 36˚F) and CRT (25˚C or 77˚F) for an unspecified length of time.
- Storage at temperatures above 25˚C (77˚F) but no more than 30˚C (86˚F) for up to 3 months.

- Storage at temperatures above 30˚C (86˚F) but no more than 40˚C (104˚F) for up to 24 hours.

10.3. Study Drug Packaging and Labeling

All packaging and labeling operations will be performed according to Good Manufacturing Practice and GCP regulations. The study drugs will be sent to authorized staff at the study site. The authorized study staff member must confirm receipt of the study drug to NBI or its designee.

Study drug will be supplied as capsules in child-resistant blistercard dispensers; each blistercard contains enough study drug for 14 days of dosing plus 3 extra dose days. The blistercards will contain capsules of valbenazine or placebo.

Each blistercard dispenser will be labeled with a single-panel label and secured with tamper evident seals. Label text will include, but is not limited to, the protocol number, dosage form, route of administration, sponsor name and address, storage condition and the statement "Caution – New Drug: Limited by Federal (or US) Law to Investigational Use."

10.4. Blinding

This study includes a double-blind, placebo-controlled treatment period during which the subject, investigator, all study site personnel, and the Sponsor will be blinded to the subject's treatment.

The randomization code will be broken for an individual subject if the subject is pregnant, experiences an SAE that the investigator feels cannot be adequately treated without knowing the identity of the subject's treatment assignment, or for regulatory reporting requirements. All attempts to contact the NBI Medical Monitor (refer to Section 11.6.3 for contact information) must be made before unblinding a subject. The unblinding form that contains the date, time, the reason the blind was broken, and name of NBI representative contacted must be completed.

10.5. Study Drug Administration

Study drug will be administered once daily, and the capsules must be swallowed with at least 250 mL of water, with or without food. The subject will be directed to take their dose at about the same time each day. If a subject forgets or is unable to take the study drug on a given day, the subject should skip that dose and resume normal dosing the following day. Subjects or their caregiver will record the date and time of study drug dosing each day on the labels provided on the study drug packaging form.

10.6. Drug Compliance and Accountability

Subjects will bring all unused study drug and empty study drug packaging material to the center at study visits for drug accountability and reconciliation by study site personnel. A compliance check will be performed by counting the capsules returned at each study visit.

The quantity of study drug dispensed, used, and returned will be recorded on a dispensing log or otherwise documented. The quantity of study drug lost or destroyed must also be accounted for and documented. The designated pharmacist or qualified personnel will be responsible for

maintaining accurate records of the quantity and dates of all study drug supplies received, dispensed, and returned.

10.7. Study Drug Return

Written documentation to account for study drug and study drug materials is mandatory; all unused study drug and study drug materials must be kept in a secure location for final accountability and reconciliation. Returned study drug and study drug material must be accounted for on a study drug return form provided by NBI or designee. The investigator must provide a written explanation for any destroyed or missing study drug or study drug materials.

Returns will be shipped to NBI or its designee at the completion of the study according to instructions provided by NBI or its designee. Study drug return forms must be completed for the shipment of returns and sent with the study drug and study drug materials. One copy of the study drug return form will be retained in the investigator's study file.

All returned study drug and study drug materials should be stored, inventoried, reconciled, and returned according to applicable state and federal regulations and study procedures.

11. ADVERSE EVENTS

All AEs, whether observed by the investigator, reported by the subject, noted from laboratory findings, or identified by other means, will be recorded from the time the subject signed the ICF until the subject's final study visit (end of Week 20 or early termination).

11.1. Definition

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

AEs include, but are not limited to: (1) a worsening or change in nature, severity, or frequency of conditions present at the start of the study; (2) subject deterioration due to primary illness; (3) intercurrent illness; and (4) drug interaction.

Subjects should be questioned in a general way, without asking about the occurrence of any specific symptom. The investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE and not the individual signs/symptoms. Following questioning and evaluation, all AEs, whether believed by the investigator to be related or unrelated to the study drug, must be documented in the subject's medical records, in accordance with the investigator's normal clinical practice and on the AE eCRF. Each AE is to be evaluated for duration, intensity, frequency, seriousness, outcome, other actions taken, and relationship to the study drug.

If at any time after baseline the subject's response to the suicidal ideation section of the C-SSRS is worse than the baseline assessment, it will be documented as an AE. All suicidal behaviors will be documented as an AE.

The following are not considered AEs:

- Continuous persistent disease/symptom present before drug administration, unless it unexpectedly progresses, or increases in severity following drug administration.
- Pregnancy.

11.2. Intensity of Adverse Events

AEs must be graded for intensity. An intensity category of mild, moderate, or severe, as defined in Table 2, must be entered on the AE eCRF. It should be noted that the term "severe" used to grade intensity is not synonymous with the term "serious."

Table 2: Intensity of Adverse Events

Grade	Intensity
Mild	An AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	An AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
Severe	An AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

11.3. Relationship to Study Drug

The investigator will document his/her opinion of the relationship of the AE to treatment with study drug using the criteria outlined in Table 3. An AE is deemed associated with the use of the study drug "if there is a reasonable possibility that the drug caused the AE" (otherwise referred to as a suspected adverse reaction). Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the AE (Title 21 CFR 312.32 [a]).

Table 3: Relationship of Adverse Events to Study Drug

Relationship	Description
Definite	A reaction that follows a reasonable temporal sequence from administration of the drug or in which the drug level has been established in body fluids or tissue; that follows a known or expected response pattern to the suspected drug; and that is confirmed by improvement on stopping or reducing the dosage of the drug, and reappearance of the reaction on repeated exposure.
Possible	An adverse event in which there is reasonable possibility that the drug caused the event. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the adverse event.
Unlikely	A reaction that follows a reasonable temporal sequence from administration of the drug; that follows a known or suspected response pattern to the suspected drug; but that could reasonably be explained by known characteristics of the subject's clinical state.
Not Related	Any event that does not meet the above criteria.

11.4. Recording Adverse Events

For enrolled subjects, each AE will be listed as a separate entry on an AE eCRF. Screen failure subjects will have AE information noted in the source documentation. The investigator (or designee) will provide information on dates and times of onset and resolution, intensity, seriousness, frequency, action(s) taken, changes in study drug usage, relationship to study drug, and outcome.

The following categories of medical events that could occur during participation in a clinical study must be reported within 24 hours to NBI or its designee:

- SAE, including death (refer to Section 11.6).
- Pregnancy (refer to Section 11.7).
- Events of suicidal behavior or suicidal ideation type 4 (active suicidal ideation with some intent to act, without specific plan) or type 5 (active suicidal ideation with specific plan and intent) based on the C-SSRS.

11.5. Post-Study Follow-Up of Adverse Events

All AEs, including clinically significant changes in ECGs, physical examination findings, or isolated clinically significant laboratory findings must be followed until the event resolves, the condition stabilizes, the event is otherwise explained, or the subject is lost to follow-up. If resolved, a resolution date should be documented on the eCRF.

AEs ongoing at the final study visit (end of Week 20 or early termination) will be followed for as long as necessary to adequately evaluate the subject's safety or until the event stabilizes or resolves or until the subject is lost to follow-up. The investigator is responsible for ensuring that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals, as is practical.

11.6. Serious Adverse Events

All SAEs will be recorded from the time the subject has signed the ICF until 30 days after the last dose of study drug or the final study visit, whichever is longer.

11.6.1. Definition of a Serious Adverse Event

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

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

11.6.2. Managing Serious Adverse Events

Subjects experiencing an SAE or an emergency situation will be examined by a physician as soon as possible. The physician in attendance will do whatever is medically needed for the safety and well-being of the subject. The subject will remain under observation as long as medically indicated. Appropriate laboratory studies will be conducted until all parameters return to normal or are otherwise explained or stable. The subject will be followed until the SAE resolves or until the subject is medically stabilized. The investigator (or designee) will notify the NBI Medical Monitor (and the IRB, if necessary) immediately (within 24 hours) of the SAE and the outcome of the SAE.

If within the time of informed consent until 30 days after the last dose of study drug or final study visit, whichever is longer, an investigator becomes aware of an SAE, then the event must be documented and reported as described in Section 11.6.3.

11.6.3. Reporting Serious Adverse Events and Other Immediately Reportable Events

Serious AEs and other immediately reportable events (defined in Section 11.4) must be reported within 24 hours of first knowledge of the event by study personnel to the NBI Medical Monitor or NBI Drug Safety and Pharmacovigilance (DSPV) Department. Reports of SAEs or pregnancies should be followed by a fax or email of the SAE or Pregnancy Form. It is important that the investigator provides his or her assessment of relationship to study drug at the time of the initial SAE report.

For SAEs or Other Immediately Reportable Events, contact DSPV:

DSPV telephone: (866) 626-7792 or (858) 617-7792

DSPV facsimile: (888) 617-7551

DSPV e-mail: cds@neurocrine.com

NBI Medical Monitor: [redacted]

11.6.4. Expedited Safety Reports

NBI or its representatives will submit an Expedited Safety Report for any suspected adverse reaction (as defined in Section 11.3) that is considered both serious and unexpected within 15 calendar days and for any unexpected fatal or life-threatening experience within 7 calendar days to the applicable regulatory authority(ies); or according to country specific regulations.

NBI or its representatives will send copies of each safety report submitted to regulatory authorities to the investigators. The safety report must be submitted to the appropriate IRB as soon as possible. Documentation of the submission to the IRB and receipt by the IRB (if applicable) must be retained for each safety report.

11.7. Pregnancy

Pregnancy is neither an AE nor an SAE unless the criteria for an SAE are met. However, all pregnancies in female subjects who received valbenazine will be followed to assess for congenital anomaly. Subjects must be counseled at all visits to continue using contraception (see inclusion criterion #2) until 30 days after the last dose of study drug for females and 90 days after the last dose of study drug for males. If at any time between the time the subject signs the ICF and the last study visit a subject believes she is pregnant, the subject will be instructed to return to the study site within 24 hours and undergo a serum pregnancy test to confirm pregnancy.

All confirmed pregnancies, in subjects who received study drug, must be immediately reported to NBI (refer to Section 11.6.3 for contact information), followed by fax or email of the pregnancy form to NBI DSPV. A first trimester ultrasound will be requested for all confirmed pregnancies. Pregnancies in subjects who received valbenazine will be followed until resolution (ie, termination [voluntary or spontaneous] or birth).

12. DOCUMENTATION OF DATA

12.1. Case Report Form

The case report form (CRF) data for this study are being collected with an electronic data capture (EDC) system (Rave®) provided by Medidata Solutions Incorporated, NY, USA. The EDC system and the study-specific eCRFs will comply with Title 21 CFR Part 11. The documentation related to the validation of the EDC system is available through the vendor, Medidata, while the validation of the study specific eCRFs will be conducted by NBI and the required documentation will be maintained in the Trial Master File.

The investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All eCRF data required by this protocol will be recorded by authorized study personnel in the EDC system, with the exception of data captured in an electronic format, which will be loaded electronically into the appropriate eCRFs. All data entered into the eCRF will be supported by source documentation. The eCRF for each subject must be reviewed by the investigator and signed on the appropriate eCRF page(s). This should be done as soon as possible after the subject completes the study.

The investigator or an authorized member of the investigator's staff will make any necessary additions/corrections to the eCRF. All change information, including the date, person performing the corrections, and reason for the change will be available via the electronic audit trail, which is part of the EDC system. The eCRFs will be reviewed periodically for completeness, legibility, and acceptability by NBI (or designee). NBI will also be allowed access to all source documents and medical records pertinent to the study in order to verify eCRF entries. The Principal Investigator will review the eCRFs for completeness and accuracy and enter his or her electronic signature on the eCRFs as evidence thereof.

Medidata will provide access to the NBI portal of the EDC system for the duration of the study through a password-protected method of internet access. Such access will be removed from investigator sites at the end of the site's participation in the study. Data from the EDC system will be archived on appropriate data media (CD-ROM, etc.) and provided to the investigator at that time as a durable record of the site’s eCRF data. Although not required, the investigator may make paper printouts from that media.

All clinical work conducted under this protocol is subject to GCP regulations. This includes an inspection by NBI and/or health authority representatives at any time. The Principal Investigator will agree to the inspection of study-related records by health authority representatives and/or NBI.

12.2. Data Capture, Review, and Validation

Data entered in the EDC system will be verified against the source data by NBI (or designee). Any discrepancies will be corrected on-line by authorized site personnel. After completion of the entry process, automated (computer-generated) logic checks will run in order to identify items such as inconsistent study dates. In addition, manual review/checks may be performed by NBI on the data. Any inconsistencies/errors/omissions identified will be sent to the site (via an electronic query) for the necessary corrections to be made to the eCRF. Once entered and saved in an eCRF, data immediately become part of the study database and are available to NBI.

12.3. Coding Dictionaries

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

13. STATISTICAL AND ANALYTICAL PLAN

Descriptive statistics and graphical methods will be used to summarize the data from this study. The term "descriptive statistics" refers to the number of subjects (n), mean, median, SD, SEM, minimum, and maximum for continuous and ordinal categorical variables; and refers to the number and percentage of subjects for categorical variables. Two-sided 95% confidence intervals will be presented for selected variables.

The analysis plan provided in this protocol represents a brief description of the planned analyses. The comprehensive statistical analysis plan (SAP) will be generated prior to final study database lock and unblinding of the treatment group assignments. The SAP may include a number of additional analyses and data summaries not described in this protocol.

13.1. Analysis Sets

Analysis sets will be defined in the SAP.

13.2. Sample Size

Approximately 120 subjects will be enrolled in this study. The 1:1 randomization to placebo or valbenazine during the double-blind, placebo-controlled treatment period will therefore provide a sample size of approximately 60 subjects in the placebo arm. The SD for the AIMS dyskinesia total score change from the end of the open-label treatment period (end of Week 8) to visits during the double-blind, placebo-controlled treatment period in the placebo treatment arm is estimated to be 4.0 based on results from the previously reported Phase 3 study NBI-98854-1304. With this SD and a sample size of 60, the overall width of a two-sided 95% confidence interval for the AIMS dyskinesia total score mean change will be approximately 2.0. The width of the confidence interval will increase to approximately 2.2 if the placebo treatment arm sample size is 50 and to approximately 2.5 if the sample size is 40.

13.3. Handling of Missing Data

In general, all available study data will be included in relevant summaries and data displays, including any available data for subjects with incomplete or missing data. Specific rules for handling missing data values (including any imputation rules) will be identified in the SAP if warranted.

13.4. Disposition of Subjects

A summary of subject disposition will be prepared that displays the number of subjects who were enrolled, who were randomized at the Week 8 visit, who completed the double-blind, placebo-controlled treatment period, and who completed the final scheduled study visit. The

number of subjects who discontinued early from the study will be displayed by reason for study discontinuation.

13.5. Demographics and Baseline Characteristics

Demographic data and baseline characteristics will be summarized with descriptive statistics or frequency tables as appropriate. Medical history will also be summarized.

13.6. Study Drug Dosing and Compliance

The number and percentage of subjects who are dose compliant (at least 80% of expected number of doses taken) will be summarized with descriptive statistics.

The number and percentage of subjects with a dose reduction will be summarized.

13.7. Persistence of Effect

Persistence of effect after randomization to either placebo or valbenazine will be based primarily on the mean changes from the randomization visit (end of Week 8) in the AIMS dyskinesia total score to visits during the double-blind, placebo-controlled treatment period. Descriptive statistics, including two-sided 95% confidence intervals for the mean, will be calculated for the changes from the end of Week 8 to each visit during the double-blind, placebo-controlled treatment period for each treatment arm. Additional measures of persistence of effect that will be summarized include AEs of TD and early discontinuation from the study due to lack of efficacy during the double-blind, placebo-controlled treatment period.

The relationship between subject clinical characteristics (including psychiatric diagnosis, age, gender, concomitant use of antipsychotic medications, and other parameters) and the persistence of effect of valbenazine during the double-blind, placebo-controlled treatment period will be evaluated using descriptive statistics and graphical methods.

13.8. Health-Related Quality of Life and Disability Data

The health-related quality of life and disability measures in this study are the EQ-5D-5L and the SDS, respectively. Descriptive statistics will be presented for each of these measures by visit.

13.9. Plasma Drug Exposure

The plasma concentrations of valbenazine and the metabolite NBI-98782 (other metabolites may be evaluated) will be summarized with descriptive statistics by dose at each visit. Concentrations below the lower limit of quantification will be set equal to zero for all plasma concentration summaries.

13.10. Safety Data

Treatment-emergent adverse events (TEAEs), categorized by MedDRA system organ class (SOC) and/or preferred term (PT) will be summarized in frequency tables. The TEAE summary tables will include the number and percentage of subjects experiencing each event.

TEAEs reported during the open-label treatment period will be summarized separately from TEAEs reported during the double-blind, placebo-controlled treatment period. Summary tables

will be presented including all TEAEs, only TEAEs that are considered to be possibly or definitely related to study drug (for the open-label treatment period only), and TEAEs according to maximum intensity.

Additional summaries will be presented for TEAEs leading to study drug dose reduction, early discontinuation from the study, SAEs, and deaths.

Clinical laboratory, vital signs, ECG, C-SSRS, and BPRS data will be summarized by visit with descriptive statistics. Potentially clinically significant (PCS) values for selected clinical laboratory and vital signs variables will be summarized.

13.11. Software

Statistical calculations and summaries will be generated using SAS software version 9.4 or later.

13.12. Interim Analysis

An interim analysis is not planned for this study.

14. REGULATORY AND ETHICAL ISSUES

14.1. General Legal References

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

14.2. Institutional Review Board

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

14.3. Protocol Adherence and Amendments

The protocol must be read thoroughly, and the instructions must be followed exactly. Any changes in the protocol will require a formal amendment. Such amendments will be agreed upon and approved in writing by the investigator and NBI. The IRB will be notified of all amendments to the protocol. Amendments to the protocol will not be implemented until written IRB approval has been received.

14.4. Required Documents

The investigator must provide to NBI or its representatives the following documents before the enrollment of any subject (originals should be kept by the investigator in the investigator's regulatory document binder):

- Signed copy of the approved protocol.
- Investigator's Brochure acknowledgement page.
- Completed and signed statement of investigator (Form FDA 1572).
- Curriculum vitae and current medical license of the investigator and subinvestigators.
- Financial disclosure information as required.
- Letter of approval from the IRB for the protocol and consent form.
- Copy of the IRB approved written ICF to be used.
- Laboratory documents (certifications/accreditations, normal ranges) if not provided by a central laboratory.

14.5. Informed Consent

All subjects will provide informed consent before the performance of any study-related procedures.

Each subject's chart will include the signed ICF for study participation. When the study treatment is completed and the eCRF has been monitored, the ICF will be kept in the investigator's central study file. Regulatory authorities may check the existence of the signed ICF in this central study folder.

14.6. Study Monitoring

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

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

14.7. Quality Assurance

The study will be conducted in accordance with NBI's standard operating procedures designed to ensure that all procedures are in compliance with GCP and FDA Guidelines and according to national law. Quality assurance audits may be performed at the discretion of NBI.

14.8. Record Retention

Federal regulations require that records of drug disposition, eCRFs, and all reports of this investigation shall be retained by the investigator for a minimum of 2 years after notification by NBI that the regulatory authorities have been notified of the study's termination, or 2 years after

approval of the marketing application. If the investigator is unable to retain the study documents for the required amount of time, NBI must be informed of the individual who will be assuming this responsibility.

14.9. Confidentiality

NBI and the clinical site affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, all data will be identified only by an identification number and, where applicable, subject's initials and birth date.

All information concerning this study and which was not previously published is considered confidential information. This confidential information shall remain the sole property of NBI; it shall not be disclosed to others without written consent of NBI; and shall not be used except in the performance of this study.

The information compiled during the conduct of this clinical study is also considered confidential and may be disclosed and/or used only by NBI as deemed necessary. To allow the use of the information derived from this clinical study and to ensure compliance with current federal regulations, the investigator is obliged to furnish NBI with the complete test results and all data compiled in this study.

15. STUDY COMMENCEMENT AND DISCONTINUATION

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

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

16. REFERENCES

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