CLINICAL STUDY PROTOCOL

Amendment No. 3 Final Version Date: 16 April 2019

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A Phase 4, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Potential for Clinical Dependence and Withdrawal Symptoms Associated with Valbenazine

Study No.: NBI-98854-TD4001

NCT03698331

Development Phase: 4

Sponsor: Neurocrine Biosciences, Inc.
12780 El Camino Real
San Diego, CA 92130
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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, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Potential for Clinical Dependence and Withdrawal Symptoms Associated with Valbenazine

PROTOCOL No.: NBI-98854-TD4001

As Agreed:

_____ _____

Principal Investigator Signature Date

PRINCIPAL INVESTIGATOR:

_____

(Print Principal Investigator Name)

CENTER:

_____

(Print Study Center Name)

Accepted for the Sponsor:

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Date

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Sponsor

Neurocrine Biosciences, Inc.
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San Diego, CA 92130

2. SYNOPSIS

Title of study: A Phase 4, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Potential for Clinical Dependence and Withdrawal Symptoms Associated with Valbenazine

Study number: NBI-98854-TD4001

Study center(s): Approximately 20 study centers in the United States

Objectives:

Primary:

- To evaluate the potential for clinical dependence and withdrawal symptoms associated with valbenazine following 4 weeks of once-daily treatment with valbenazine or placebo.

Secondary:

- To evaluate the efficacy of valbenazine administered once daily for up to 4 weeks.
- To evaluate the safety and tolerability of valbenazine administered once daily for up to 4 weeks.

Study design: This is a Phase 4, randomized, double-blind, placebo-controlled study to evaluate the potential for clinical dependence and withdrawal symptoms associated with valbenazine. Approximately 80 medically stable male and female subjects (the proportion of males and females will be consistent with that of the patient population) with neuroleptic-induced tardive dyskinesia (TD) will be enrolled.

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).

On Day -1, eligible subjects will be randomized (1:1) to 1 of the 2 treatment arms (randomization will be stratified by study site):

- Valbenazine (40 mg for the first week followed by 80 mg for 3 weeks) for the first 4 weeks of the double-blind treatment period followed by placebo for the last 3 weeks of the double-blind treatment period.
- Placebo for the 7 weeks of the double-blind treatment period.

An Interactive Web Response System (IWRS) will be used to maintain the study blind. Study drug will be self-administered at home (in the presence of the subject's caregiver, if applicable) beginning on Day 1 of Week 1. At any time, the investigator can decrease the subject's dose to 40 mg if the subject is unable to tolerate the 80 mg dose (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 (or placebo) will be discontinued from the study.

Study sites will call subjects at the end of Weeks 2 and 3 to remind them to take their study drug daily. Visits during Weeks 1 and 4 have a window of ±3 days, visits during Week 5 have no window, and visits during Weeks 6 and 7 have a window of ±1 day.

A blood sample will be collected from randomized subjects on Day -1 to determine their cytochrome P450 (CYP) 2D6 genotype. Clinical dependence and withdrawal symptoms, efficacy, pharmacokinetics (PK), safety, and tolerability will be assessed at scheduled times throughout the study.

Study population: Approximately 80 medically stable male and female subjects (the proportion of males and females will be consistent with that of the patient population) aged 18 to 65 years (inclusive) with clinical diagnoses of schizophrenia or schizoaffective disorder with neuroleptic-induced TD or mood disorder with neuroleptic-induced TD will be enrolled. Subjects must be psychiatrically stable as determined clinically by the investigator, including a Brief Psychiatric Rating Scale (BPRS) score of <50 at screening and baseline (Day -1).

Duration of treatment and study participation: The expected duration of study participation for each subject is approximately 13 weeks, including up to 6 weeks of screening and 7 weeks of double-blind study drug treatment.

Investigational product, dosage, and mode of administration: Valbenazine will be supplied as capsules containing 20 or 40 mg of valbenazine (free base equivalent as the ditosylate salt). The doses that will be used in this study are: 40 mg once daily taken as two valbenazine 20 mg capsules and 80 mg once daily taken as two valbenazine 40 mg capsules. Subjects will swallow the capsules with at least 250 mL of water and can take the study medication with or without food each morning at approximately the same time (between 0700 and 1000 hours).

Reference therapy, dosage, and mode of administration: Matching placebo capsules are identical in appearance and will be orally administered. Subjects will swallow the 2 placebo capsules with at least 250 mL of water and can take the study medication with or without food each morning at approximately the same time (between 0700 and 1000 hours).

Criteria for evaluation:

Clinical dependence and withdrawal symptoms:

The modified Cocaine Selective Severity Assessment (mCSSA) and Physician Withdrawal Checklist-20 (PWC-20) will be used to evaluate clinical dependence and withdrawal symptoms and will be administered at baseline (Day -1), at the end of Week 4, Week 5 (Days 1, 3, 5, and 7), Week 6 (Days 2, 4, and 7), Week 7 (Days 2 and 4), and at the final study visit (Week 7 Day 7 or upon early termination).

The Epworth Sleepiness Scale (ESS), Hamilton Anxiety Rating Scale (HAM-A), and withdrawal-related adverse events (AEs) will also be used to assess for clinical dependence and withdrawal symptoms.

Efficacy:

The Clinical Global Impression-Tardive Dyskinesia-Improvement (CGI-TD-I) and Clinical Global Impression-Tardive Dyskinesia-Severity (CGI-TD-S) will be used to rate the investigator's (or designee) assessments of the subject's overall improvement and severity of TD, respectively. The CGI-TD-I will be administered during the treatment period (end of Week 4), and at the final study visit (Week 7 Day 7 or upon early termination). The CGI-TD-S will be administered at baseline (Day -1), during the treatment period (end of Week 4, Day 7 of Weeks 5 and 6), and at the final study visit (Week 7 Day 7 or upon early termination).

Plasma Drug Exposure:

Blood samples to evaluate plasma concentrations of valbenazine and the metabolite NBI-98782 (other metabolites may be evaluated) will be collected at Weeks 1 and 4.

Safety:

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

- AEs
- Clinical laboratory tests (hematology, serum chemistry, and urinalysis)
- Vital signs (including orthostatic blood pressure and pulse)
- Physical examinations
- 12-lead electrocardiogram (ECG)
- Suicidal ideation and behavior, evaluated using the Columbia-Suicide Severity Rating Scale (C-SSRS)
- Drug-induced akathisia and extrapyramidal symptoms (EPS), evaluated using the Barnes Akathisia Rating Scale (BARS) and Simpson-Angus Scale (SAS)
- Montgomery-Asberg Depression Rating Scale (MADRS).

Statistical methods: The primary assessment of withdrawal will be the number of subjects with withdrawal-related AEs; differences between treatment groups will be tested for statistical significance using Fisher's exact test. The secondary assessment of withdrawal will be the percentage of subjects in each treatment group who experience an increase on the PWC-20 by 5 new symptoms of moderate or severe degree or a worsening of symptoms by 2 points during Weeks 5 to 7 compared with Week 4. Other assessments of withdrawal will be the mean worst scores per treatment group on the PWC-20 and mCSSA, which will be summarized using descriptive statistics; results from the ESS and the HAM-A will be summarized using descriptive statistics. Efficacy, PK, and safety data will be summarized using descriptive statistics.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
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
BARS	Barnes Akathisia Rating Scale
BMI	body mass index
BPRS	Brief Psychiatric Rating Scale
CFR	Code of Federal Regulations
CGI-TD-I	Clinical Global Impression-Tardive Dyskinesia-Improvement
CGI-TD-S	Clinical Global Impression-Tardive Dyskinesia-Severity
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
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DSPV	Drug Safety and Pharmacovigilance
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EDTA K_2	dipotassium ethylenediaminetetraacetic acid
EPS	extrapyramidal symptoms
EPSE	extrapyramidal side effects
ESS	Epworth Sleepiness Scale
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GGT	gamma-glutamyl transferase
HAM-A	Hamilton Anxiety Rating Scale
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/IEC	Institutional Review Board/Independent Ethics Committee
IWRS	Interactive Web Response System
MADRS	Montgomery-Asberg Depression Rating Scale
MAOI	monoamine oxidase inhibitor
mCSSA	modified Cocaine Selective Severity Assessment
MedDRA	Medical Dictionary for Regulatory Activities
NBI	Neurocrine Biosciences, Inc.
PCR	polymerase chain reaction
PK	pharmacokinetic
prn	as needed
PWC-20	Physician Withdrawal Checklist-20
QTcF	corrected QT interval using Fridericia's formula
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	Simpson-Angus Scale
SIGMA	Structured Interview Guide for the MADRS
$t_{½}$	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 (GCP): 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/Independent Ethics Committees (IRBs/IECs) 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 (DSM-5) 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 versus time concentration 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 (EPS; 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 present study is a Phase 4, randomized, double-blind, placebo-controlled study to evaluate the potential for clinical dependence and withdrawal symptoms associated with valbenazine in medically stable subjects with schizophrenia, schizoaffective disorder, or mood disorder and TD. In order to maintain the study blind, subjects will be randomized to receive placebo throughout the double-blind treatment period, or valbenazine for the first 4 weeks of the double-blind treatment period followed by placebo for the remaining 3 weeks.

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

6. STUDY OBJECTIVES

Primary:

- To evaluate the potential for clinical dependence and withdrawal symptoms associated with valbenazine following 4 weeks of once-daily treatment with valbenazine or placebo.

Secondary:

- To evaluate the efficacy of valbenazine administered once daily for up to 4 weeks.
- To evaluate the safety and tolerability of valbenazine administered once daily for up to 4 weeks.

7. STUDY DESIGN

This is a Phase 4, randomized, double-blind, placebo-controlled study to evaluate the potential for clinical dependence and withdrawal symptoms associated with valbenazine. Approximately 80 medically stable male and female subjects (the proportion of males and females will be consistent with that of the patient population) with neuroleptic-induced TD will be enrolled.

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 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).

On Day -1, eligible subjects will be randomized (1:1) to 1 of the 2 treatment arms (randomization will be stratified by study site):

- Valbenazine (40 mg for the first week followed by 80 mg for 3 weeks) for the first 4 weeks of the double-blind treatment period followed by placebo for the last 3 weeks of the double-blind treatment period.
- Placebo for the 7 weeks of the double-blind treatment period.

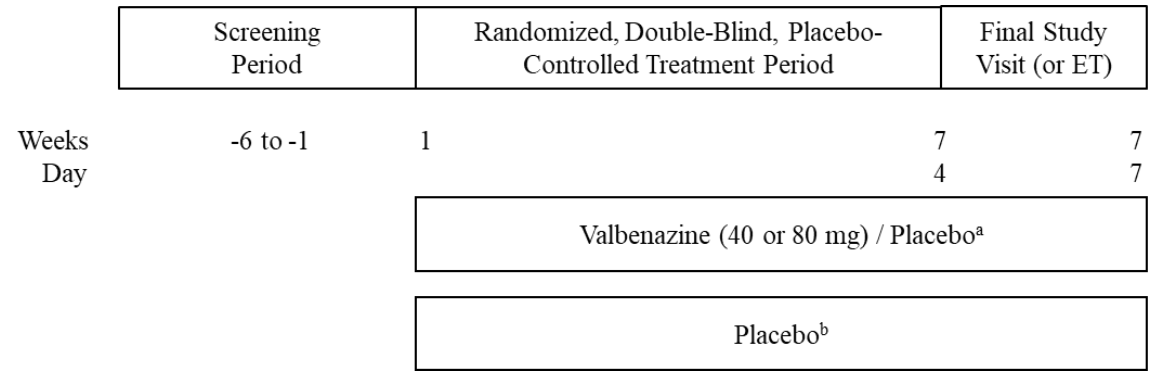
An Interactive Web Response System (IWRS) will be used to maintain the study blind. Study drug will be self-administered at home (in the presence of the subject's caregiver, if applicable) beginning on Day 1 of Week 1. At any time, the investigator can decrease the subject's dose to 40 mg if the subject is unable to tolerate the 80 mg dose (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 (or placebo) will be discontinued from the study.

Study sites will call subjects at the end of Weeks 2 and 3 to remind them to take their study drug daily. A final study visit will be conducted at Week 7 Day 7 or at early termination. Visits during Weeks 1 and 4 have a window of ±3 days, visits during Week 5 have no window, and visits during Weeks 6 and 7 have a window of ±1 day.

A blood sample will be collected from randomized subjects on Day -1 to determine their CYP2D6 genotype. Clinical dependence and withdrawal symptoms, efficacy, pharmacokinetics (PK), safety, and tolerability will be assessed at scheduled times throughout the study.

A schematic of the study design is provided in Figure 1.

Figure 1: Study Design Schematic



ET=early termination.
[a] Subjects will receive valbenazine (40 mg for 1 week increased to 80 mg for 3 weeks) for 4 weeks followed by placebo for 3 weeks.
[b] Subjects will receive placebo for 7 weeks.

8. STUDY POPULATION

8.1. Subject Inclusion Criteria

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

1. Be male or female aged 18 to 65 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 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 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 at baseline (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, 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 typical parkinsonism associated with EPS or extrapyramidal side effects (EPSE).
6. 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 new or discontinued medications for a minimum of 30 days before baseline [Day -1]), and these doses are expected to remain stable during the study. 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).

7. Subjects (eg, 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 baseline (Day -1).
8. Be in good general health and expected to complete the clinical study as designed.
9. 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.)
10. Have adequate hearing, vision, reading, and language skills to perform the procedures specified in the protocol.
11. 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.
12. Have a negative urine drug screen (UDS) (negative for amphetamines, methamphetamine, barbiturates, benzodiazepines, phencyclidine, cocaine, opiates, methadone, tricyclic antidepressants, or cannabinoids) at screening (central laboratory results) and baseline (Day -1) (UDS kit results conducted at the study site) except for any subject receiving a stable dose (ie, no as needed [prn] use) of benzodiazepines, opiates, or tricyclic antidepressants. 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, and has a negative UDS after retesting a minimum of 4 weeks after the initial positive result.
13. Have a negative alcohol breath test at screening and baseline (Day -1).
14. Be willing to provide authorization for access to personal health information in conjunction with US Health Insurance Portability and Accountability Act (HIPAA).

8.2. Subject Exclusion Criteria

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 baseline (Day -1).
2. Have a Simpson-Angus Scale (SAS) score ≥3 on two or more items at screening or baseline (Day -1), excluding Items 8 and 10.
3. Have a known history of substance dependence, or substance (drug) or alcohol abuse within the 3 months prior to baseline (Day -1) (nicotine and caffeine dependence are not exclusionary), as defined in the DSM (eg, DSM-IV or -5).
4. Have a Brief Psychiatric Rating Scale (BPRS) total score of ≥50 at screening or baseline (Day -1).

5. Have a significant risk of suicidal or violent behavior. Subjects with any 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 Columbia-Suicide Severity Rating Scale (C-SSRS) in the 3 months prior to screening (using Baseline/Screening version) or baseline (Day -1) (using Since Last Visit version) will be excluded.
6. Have a known history of neuroleptic malignant syndrome.
7. Have a known history of long QT syndrome or cardiac arrhythmia.
8. Have a screening or baseline (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.
9. Receive any excluded concomitant medication as detailed in Section 9.9.1.
10. 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.
11. Have a hematologic malignancy or solid tumor diagnosed within 3 years prior to screening, with the exception of localized skin cancer or carcinoma in situ of the cervix.
12. 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 $<100,000/mm^3$.
13. Have other laboratory results not within the laboratory's reference range and deemed by the investigator to be clinically significant.
14. 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, and total bilirubin in exclusion criterion #10.
15. Have received an investigational drug within 30 days or 5 half-lives (if known), whichever is longer, prior to baseline (Day -1) or plan to use an investigational drug during the study.
16. Have had a blood loss ≥550 mL or donated blood within 30 days prior to baseline (Day -1).
17. Have an allergy, hypersensitivity, or intolerance to VMAT2 inhibitors (eg, tetrabenazine, deutetrabenazine).
18. Have had previous experience with valbenazine (INGREZZA or NBI-98854) or had previously participated in a valbenazine clinical study.

19. Are currently pregnant or lactating.

8.3. Subject Identification and Replacement of Subjects

Subjects will be identified by their unique subject number and initials (first, middle, last; a hyphen may be used if a subject does not have a middle name). 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 will not be replaced.

8.4. Randomization

On Day -1, eligible subjects will be randomized (1:1) to 1 of the 2 treatment arms (randomization will be stratified by study site):

- Valbenazine (40 mg for the first week followed by 80 mg for 3 weeks) for the first 4 weeks of the double-blind treatment period followed by placebo for the last 3 weeks of the double-blind treatment period.
- Placebo for the 7 weeks of the double-blind treatment period.

The subjects, investigators, and Sponsor will be blinded to the treatment assignment (programmed on the IWRS).

9. STUDY EVALUATIONS

9.1. Schedule of Assessments

A schedule of assessments is shown in Table 1. Subjects will provide written informed consent before any study-related procedures are performed. 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 case report forms (CRFs).

Table 1: Schedule of Assessments

Procedure	Screening Period	Baseline	Double-Blind Treatment Period											Final Study Visit/ ET[c]
Week[a]	**-6 to -1**	**Day -1**	**1**	**4**	**5**				**6**			**7**		**7**
Day[b]	--	--	--	--	**1**	**3**	**5**	**7**	**2**	**4**	**7**	**2**	**4**	**7**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
UBACC / Informed consent[d]	X													
Inclusion/exclusion criteria	X	update												
Medical history	X	update												
Physical examination (including weight)	X	X	X	X				X			X			X
Height	X													
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[e]	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
Genotype blood sample		X												
Urine drug screen[h]	X	X		X					X			X		
Alcohol breath test[i]	X	X		X					X			X		
PK plasma sample[j]			X	X										
Randomization		X												
CGI-TD-S		X		X				X			X			X
CGI-TD-I				X										X
C-SSRS	X	X		X										X
BPRS	X	X												
BARS		X		X										X
SAS	X	X		X										X
ESS	X	X		X	X	X	X	X	X	X	X	X	X	X
HAM-A	X	X		X	X	X	X	X	X	X	X	X	X	X
MADRS	X	X		X										X
mCSSA and PWC-20		X		X	X	X	X	X	X	X	X	X	X	X
Study drug dosing at home[k]			X	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug		X	X	X							X			
Study drug accountability[l]			X	X							X			X
AE monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Call to subjects[m]			X											

Definitions and footnotes are on the following page.

AE=adverse event; BARS=Barnes Akathisia Rating Scale; BPRS=Brief Psychiatric Rating Scale; CGI-TD-I=Clinical Global Impression-Tardive Dyskinesia-Improvement; CGI-TD-S=Clinical Global Impression-Tardive Dyskinesia-Severity; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ESS=Epworth Sleepiness Scale; ET=early termination; HAM-A=Hamilton Anxiety Rating Scale; HBsAg=hepatitis B surface antigen; HCV-Ab=hepatitis C virus antibody; HIV-Ab=human immunodeficiency virus antibody; MADRS=Montgomery-Asberg Depression Rating Scale; mCSSA=modified Cocaine Selective Severity Assessment; PK=pharmacokinetic; PWC-20=Physician Withdrawal Checklist-20; QTcF=corrected QT interval using Fridericia's formula; s=serum; SAS=Simpson-Angus Scale; u=urine; UBACC=University of California, San Diego Brief Assessment of Capacity to Consent.

a. Day 1 of Week 1 (ie, the day after Day -1) is the first day of dosing; study drug will be self-administered at home and subjects are not required to come to the study site. Visits during Weeks 1 and 4 have a window of ±3 days, visits during Week 5 have no window, and visits during Weeks 6 and 7 have a window of ±1 day. As much as possible, study visits should be scheduled at approximately the same time of day.
b. Day 1 of Week 5, for example, is the first day of all subjects receiving placebo treatment.
c. Final study visit for subjects who complete the study (or upon early termination).
d. The UBACC will be used to determine whether the subject has the capacity to provide informed consent. All subjects must provide informed consent prior to any study-related procedures.
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, and 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. Serum pregnancy tests will be conducted at screening. A urine pregnancy test will be conducted at baseline (Day -1) and subsequent visits. The urine pregnancy test result at baseline (Day -1) will be used to confirm eligibility.
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, baseline (Day -1), and Week 4 by the central lab. In addition, a urine drug screen kit provided by the central lab will used at the site at baseline (Day -1) to confirm eligibility, and at Week 6 (Day 2), and Week 7 (Day 2). Subjects who test positive for cannabinoids during screening should retest 4 weeks from last exposure to cannabinoids (must be within screening window). A urine drug screen using a kit provided by the central laboratory may be conducted at the clinical site at any time during the study if the subject is suspected of substance or drug abuse.
i. Subjects should not consume alcohol within 24 hours of their visits at Week 4, Week 6 (Day 2), or Week 7 (Day 2).
j. Subjects will be asked to record and provide dosing times on the days during the treatment period when blood PK samples are collected.
k. Subjects will self-administer study drug daily beginning on Day 1 of Week 1 (at approximately the same time each day, between 0700-1000 hours) at home in the presence of their caregiver (if applicable). Subject or caregiver will record the daily date and time of dosing on the drug packaging form provided.
l. At the end of Weeks 1, 4, 6, and 7 (or early termination), 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.
m. Study sites will call subjects at the end of Weeks 2 and 3 to remind them to take their study drug daily.

9.2. Screening and Baseline Assessments

9.2.1. Genotyping

A blood sample will be collected from subjects for the analysis of CYP2D6 status (ie, normal, intermediate, poor, or ultrarapid metabolizers) on Day -1. Approximately 2 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 samples will be stored at approximately -20°C within approximately 15 minutes of collection. 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.

9.2.2. 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 at baseline (Day -1), and subjects must have a BPRS total score <50 to be eligible for study participation (see exclusion criterion #4). If possible, the same person should administer and score the scales at all timepoints.

9.3. Clinical Dependence and Withdrawal Symptoms Assessments

9.3.1. Modified Cocaine Selective Severity Assessment

The modified Cocaine Selective Severity Assessment (mCSSA) is a validated instrument that measures early cocaine abstinence signs and symptoms (Kampman et al., 1998). The mCSSA is an 18-item instrument primarily drawn from symptoms commonly reported in the literature as being associated with early cocaine abstinence, including depression, fatigue, anhedonia, anxiety, irritability, sleep disturbance, and inability to concentrate. The instrument includes additional symptoms such as paranoia, carbohydrate craving, bradycardia, and suicidality. Items are rated on scales of 0 to 7 or 0 to 8, with separate scale descriptions for each item. The scale has been modified to be specific to study drug (valbenazine or placebo) instead of cocaine; specifically, “cocaine” was replaced with “study drug” in question #4 and in the 2 visual analog scales.

The mCSSA will be administered by the investigator or qualified study site personnel at baseline (Day -1), Weeks 4, 5 (Days 1, 3, 5, and 7), 6 (Days 2, 4, and 7), 7 (Days 2 and 4), and the final study visit (Week 7 Day 7 or early termination). If possible, the same person should administer the mCSSA for an individual subject at all timepoints.

9.3.2. Physician Withdrawal Checklist-20

The Physician Withdrawal Checklist-20 (PWC-20) is a validated 20-item physician-rated instrument that assesses potential symptoms of withdrawal on a severity scale in the following areas: gastrointestinal, mood, sleep, motor, somatic, perception, and cognition (Rickels et al., 2008). Items are rated on a scale from 0 to 3, with total scores ranging from 0 to 60.

The PWC-20 will be administered by the investigator or qualified study site personnel at baseline (Day -1), Weeks 4, 5 (Days 1, 3, 5, and 7), 6 (Days 2, 4, and 7), 7 (Days 2 and 4), and the final study visit (Week 7 Day 7 or early termination). If possible, the same person should administer the PWC-20 for an individual subject at all timepoints.

9.3.3. Epworth Sleepiness Scale

The Epworth Sleepiness Scale (ESS) is a validated instrument to assess subject's sleepiness (Chervin et al., 1997). The instrument lists 8 daytime situations in which the subject rates his/her tendency to become sleepy on a scale from 0 (would never doze) to 3 (high chance of dozing). The total score ranges from 0 to 24.

Subjects will complete the ESS at screening, baseline (Day -1), Weeks 4, 5 (Days 1, 3, 5, and 7), 6 (Days 2, 4, and 7), 7 (Days 2 and 4), and the final study visit (Week 7 Day 7 or early termination).

9.3.4. Hamilton Anxiety Rating Scale

The Hamilton Anxiety Rating Scale (HAM-A) is a validated, clinician-rated instrument to evaluate the severity of anxiety (Maier et al., 1988). The HAM-A is composed of 14 items, each of which is scored from 0 (not present) to 4 (very severe). The total score ranges from 0 to 56.

The investigator or other qualified site personnel will administer the HAM-A at screening, baseline (Day -1), Weeks 4, 5 (Days 1, 3, 5, and 7), 6 (Days 2, 4, and 7), 7 (Days 2 and 4), and the final study visit (Week 7 Day 7 or early termination). If possible, the same person should administer and score the scale at all timepoints.

9.4. Efficacy Assessments

9.4.1. Clinical Global Impression-Tardive Dyskinesia-Improvement

The Clinical Global Impression-Tardive Dyskinesia-Improvement (CGI-TD-I) scale will be used to assess overall improvement since the initiation of study drug dosing on a 7-point scale (range; 1=very much improved to 7=very much worse). The investigator or qualified study site personnel will rate the scale at the scheduled times. If possible, the same person should rate the CGI-TD-I at all visits.

CGI-TD-I will be assessed at Week 4 and the final study visit (Week 7 Day 7 or early termination).

9.4.2. Clinical Global Impression-Tardive Dyskinesia-Severity

The Clinical Global Impression-Tardive Dyskinesia-Severity (CGI-TD-S), which is based on a 7-point scale (range; 1=normal, not at all ill to 7=among the most extremely ill patient), will be used to rate the overall global severity of TD. This scale is a modification of a scale developed by the Psychopharmacology Research Branch of the National Institute of Mental Health (Guy, 1976).

The investigator or qualified study site personnel will rate the scale at the scheduled times. If possible, the same person should rate the CGI-TD-S at all visits.

The CGI-TD-S will be assessed at baseline (Day -1), Weeks 4, 5 (Day 7), 6 (Day 7), and the final study visit (Week 7 Day 7 or early termination).

9.5. Pharmacokinetics Assessment

Blood samples to determine plasma concentrations of valbenazine and its metabolite NBI-98782 (other metabolites may be evaluated) will be collected at the end of Weeks 1 and 4. Subjects will be asked to record and provide dosing times on the days when PK blood samples are collected. The exact time of collection will be recorded on the eCRF.

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. Additional 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. Vital Sign Measurements

Vital sign measurements will include orthostatic systolic and diastolic blood pressure, orthostatic pulse rate, respiratory rate (recorded supine only), 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 obtained before any scheduled blood sample collection.

Vital sign measurements will be collected during screening, at baseline (Day -1), Weeks 1, 4, 5 (Days 1, 3, 5, and 7), 6 (Days 2, 4, and 7), 7 (Days 2 and 4), and the final study visit (Week 7 Day 7 or early termination).

9.6.2. Medical History

A medical history will be taken at the screening visit and updated at baseline (Day -1) and as needed throughout the study.

The subject's psychiatric history will be documented and will include the subject's age at first diagnosis of schizophrenia, schizoaffective disorder, or mood disorder, and age at TD diagnosis. If necessary, subject age at onset can be estimated by the investigator based upon available clinical information.

9.6.3. 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, baseline (Day -1), Weeks 1, 4, 5 (Day 7), 6 (Day 7), and the final study visit (Week 7 Day 7 or early termination). Height will be measured at screening only. Height and weight will be measured with subjects not wearing shoes.

9.6.4. 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 will be conducted at screening, baseline (Day -1), Weeks 1 and 4, and the final study visit (Week 7 Day 7 or early termination).

9.6.5. Clinical Laboratory Assessments

All clinical laboratory assessments will be performed by a central laboratory. 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. 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 2 mL for genotyping. Approximate total blood sample volume per subject is 25 mL (including PK samples).

The following clinical safety laboratory assays will be performed at screening, baseline (Day -1), Week 4, and the final study visit (Week 7 Day 7 or early termination):

Hematology: complete blood count including WBC count with differential, red blood cell (RBC) count, hemoglobin, hematocrit, and platelet count, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), red cell distribution width (RDW).

Clinical Chemistry: sodium, potassium, calcium, magnesium, phosphorus, 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: specific gravity, nitrite, ketones, protein, urobilinogen, glucose, bilirubin, leukocyte esterase, occult blood, and pH; microscopic examination of sediment will be performed only if the results of the urinalysis dipstick evaluation are positive for nitrite, 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 and reflex PCR testing at screening.

UDS 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, baseline (Day -1), and Week 4 by a certified central laboratory. In addition, a UDS will be conducted at the clinical site at baseline (Day -1) using a UDS kit provided by the central laboratory and the results will be used to confirm study eligibility, and at Week 6 (Day 2) and Week 7 (Day 2). Subjects who test positive for cannabinoids during screening should retest 4 weeks from last exposure to cannabinoids (must be within screening window). A UDS using a kit provided by the central laboratory may be conducted at the clinical site at any time during the study if the subject is suspected of substance or drug abuse.

The alcohol breath test will be performed at screening, baseline (Day -1), Week 4, Week 6 (Day 2), and Week 7 (Day 2).

Pregnancy Test: 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 at baseline (Day -1; a negative test result is required to be eligible for the study) and at Weeks 1, 4, 5 (Day 7), 6 (Day 7), and the final study visit (Week 7 Day 7 or early termination).

9.6.6. 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 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) in the 3 months before screening or baseline (Day -1) based on the C-SSRS should be excluded (see exclusion criterion #5).

The C-SSRS will be administered and scored by the investigator or qualified study site personnel at screening, baseline (Day -1), Week 4, and the final study visit (Week 7 Day 7 or early termination). Of note, the Since Last Visit version of the C-SSRS will be administered at Week 4 and at the final study visit (Week 7 Day 7 or early termination), but the lookback period will be since the last C-SSRS assessment, not since the subject's last visit. If possible, the same person should administer and score the scale at all timepoints.

9.6.7. Barnes Akathisia Rating Scale

The Barnes Akathisia Rating Scale (BARS) is a validated 4-item scale to assess the presence and severity of drug-induced akathisia (Barnes, 1989). This scale includes both objective items (eg, observed restlessness) and subjective items (eg, subject's awareness of restlessness and related distress), together with a global assessment of akathisia. Global assessment is made on a scale of 0 to 5 (0=absent; 1=questionable; 2=mild akathisia; 3=moderate akathisia; 4=marked akathisia; 5=severe akathisia).

The investigator or other qualified site personnel will administer and score the BARS at the scheduled times. The BARS will be administered at baseline (Day -1), Week 4, and the final study visit (Week 7 Day 7 or early termination). If possible, the same person should administer and score this scale at all timepoints.

9.6.8. Simpson-Angus Scale

The SAS is a validated 10-item scale to evaluate the presence and severity of drug-induced parkinsonism and other extrapyramidal symptoms (Simpson and Angus, 1970). The 10 items focus on clinician-assessed EPSE and each item is rated on a 0 to 4 scale of increasing severity with definitions given for each anchor point. The SAS will also be used as a screening tool; subjects will be excluded if they have a score ≥3 on two or more items at screening or baseline (Day -1), excluding Items 8 and 10 (see exclusion criterion #2).

The investigator or other qualified site personnel will administer and score the scale at screening, baseline (Day -1), Week 4, and the final study visit (Week 7 Day 7 or early termination). If possible, the same person should administer and score the scales at all timepoints.

9.6.9. Montgomery-Asberg Depression Rating Scale using the Structured Interview Guide for the MADRS

The Montgomery-Asberg Depression Rating Scale (MADRS) is a validated rating scale designed to measure changes in the severity of depressive symptoms (Montgomery and Asberg, 1979). The MADRS consists of 10 items scored on a 7-point scale (0 to 6) with increasing number value indicating increasing severity for each item with anchor points provided at 2-point intervals. Scoring is based on a structured clinical interview following the Structured Interview Guide for the MADRS (SIGMA; Williams and Kobak, 2008).

The investigator or other qualified site personnel will administer and score the scale at screening, baseline (Day -1), Week 4, and the final study visit (Week 7 Day 7 or early termination). If possible, the same person should administer and score the scale at all timepoints.

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. As much as possible, study visits should be scheduled at approximately the same time of day.

9.7.1. Screening (Week -6 to -1)

Informed Consent Process: The ICF will be reviewed with subjects. The UBACC will then be administered (Jeste et al., 2007). 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:

- 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 a serum pregnancy test (β-hCG) for 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 and UDS.
- Perform alcohol breath test.
- Administer the C-SSRS (Screening/Baseline version).
- Administer the BPRS.
- Administer the SAS.
- Administer the ESS.
- Administer the HAM-A.
- Administer the MADRS.
- AE monitoring.
- Record prior and concomitant medications.

Subjects will be asked to refrain from taking prohibited medications as specified in Section 9.9.

9.7.2. 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 for female subjects of childbearing potential.
- Collect blood sample for hematology and clinical chemistry.
- Collect urine sample for urinalysis.
- Collect blood sample for genotyping.
- Perform UDS (using the UDS kit to confirm eligibility and collect central laboratory sample).
- Perform alcohol breath test.
- Randomization.
- Administer the CGI-TD-S.
- Administer the C-SSRS (Since Last Visit version).
- Administer the BPRS.
- Administer the BARS.
- Administer the SAS.
- Administer the ESS.
- Administer the HAM-A.
- Administer the MADRS.
- Administer the mCSSA.
- Administer the PWC-20.
- Dispense study drug.
- AE monitoring.
- Record concomitant medications.

Subjects will be instructed to begin taking study drug the following day (ie, Week 1 Day 1) as detailed in Section 10.5.

9.7.3. Double-Blind Treatment Period (Weeks 1 to 7)

Study sites will call subjects at the end of Weeks 2 and 3 to remind them to take their study drug daily.

9.7.3.1. Week 1 (±3 days)

The following study evaluations and procedures will be performed at the end of Week 1:

- 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 for female subjects of childbearing potential.
- Collect PK blood sample.
- Dispense study drug.
- Study drug accountability.
- AE monitoring.
- Record concomitant medications.

9.7.3.2. Week 4 (±3 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 for female subjects of childbearing potential.
- Collect blood sample for hematology and clinical chemistry.
- Collect urine sample for urinalysis.
- Perform UDS.
- Perform alcohol breath test.
- Collect PK blood sample.
- Administer the CGI-TD-S.
- Administer the CGI-TD-I.
- Administer the C-SSRS (Since Last Visit version; lookback period to Day -1 [baseline]).
- Administer the BARS.
- Administer the SAS.
- Administer the ESS.
- Administer the HAM-A.
- Administer the MADRS.
- Administer the mCSSA.
- Administer the PWC-20.
- Dispense study drug.
- Study drug accountability.
- AE monitoring.
- Record concomitant medications.

9.7.3.3. Week 5, Days 1, 3, 5, and 7

The following study evaluations and procedures will be performed on Week 5, Days 1, 3, 5, and 7:

- Physical examination (Day 7 only).
- Collect vital signs, including orthostatic systolic and diastolic blood pressures, orthostatic pulse rate, respiratory rate, and oral body temperature.
- Perform a urine pregnancy test for female subjects of childbearing potential (Day 7 only).
- Administer the CGI-TD-S (Day 7 only).
- Administer the ESS.
- Administer the HAM-A.
- Administer the mCSSA.
- Administer the PWC-20.
- AE monitoring.
- Record concomitant medications.

9.7.3.4. Week 6, Days 2, 4, and 7 (±1 day)

The following study evaluations and procedures will be performed on Week 6, Days 2, 4, and 7:

- Physical examination (Day 7 only).
- Collect vital signs, including orthostatic systolic and diastolic blood pressures, orthostatic pulse rate, respiratory rate, and oral body temperature.
- Perform a urine pregnancy test for female subjects of childbearing potential (Day 7 only).
- Perform UDS (Day 2 only).
- Perform alcohol breath test (Day 2 only).
- Administer the CGI-TD-S (Day 7 only).
- Administer the ESS.
- Administer the HAM-A.
- Administer the mCSSA.
- Administer the PWC-20.
- Dispense study drug (Day 7 only).
- Study drug accountability (Day 7 only).
- AE monitoring.
- Record concomitant medications.

9.7.3.5. Week 7, Days 2 and 4 (±1 day)

The following study evaluations and procedures will be performed on Week 7, Days 2 and 4:

- Collect vital signs, including orthostatic systolic and diastolic blood pressures, orthostatic pulse rate, respiratory rate, and oral body temperature.

- Perform UDS (Day 2 only).
- Perform alcohol breath test (Day 2 only).
- Administer the ESS.
- Administer the HAM-A.
- Administer the mCSSA.
- Administer the PWC-20.
- AE monitoring.
- Record concomitant medications.

9.7.4. Final Study Visit (Week 7 Day 7 [±1 day] or Early Termination)

The following study evaluations and procedures will be performed at Week 7 Day 7 or 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 for female subjects of childbearing potential.
- Collect blood sample for hematology and clinical chemistry.
- Collect urine sample for urinalysis.
- Administer the CGI-TD-S.
- Administer the CGI-TD-I.
- Administer the C-SSRS (Since Last Visit version; lookback period to Week 4).
- Administer the BARS.
- Administer the SAS.
- Administer the ESS.
- Administer the HAM-A.
- Administer the MADRS.
- Administer the mCSSA.
- Administer the PWC-20.
- Study drug accountability.
- AE monitoring.
- Record concomitant medications.

9.8. Study Duration

The expected duration of study participation for each subject is approximately 13 weeks, including up to 6 weeks of screening and 7 weeks of double-blind study drug treatment.

9.9. Prohibitions and Restrictions

9.9.1. Prior and Concomitant Medications

All prescription and over-the-counter (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.

Medications to treat psychiatric and medical conditions: All coexistent diseases or conditions will be treated in accordance with prevailing medical practice. Maintenance medication(s) for schizophrenia or schizoaffective disorder, mood disorders, and other nonprohibited concurrent medications should be at a stable dose (including no changes to the dose and frequency of ongoing medications and no new or discontinued medications) for a minimum of 30 days before baseline (Day -1), and these doses are expected to remain stable during the study. Benzodiazepines must be at a stable dose (ie, no prn use) for 2 weeks before baseline (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).

Prohibited medications: The following medications are prohibited from 30 days prior to baseline (Day -1) (unless otherwise stated) until the final study visit (or early termination) as described below:

- **Antiemetics:** Metoclopramide, prochlorperazine, and promethazine are prohibited.
- **CYP3A4 inducers:** Strong inducers of CYP3A4 (eg, phenytoin, phenobarbital, rifabutin, rifampin, primidone, St. John's Wort) are prohibited.
- **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.
- **VMAT2 Inhibitors:** VMAT2 inhibitor medications (eg, tetrabenazine, deutetrabenazine, reserpine) are prohibited (except for valbenazine administered per the current protocol).

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

9.9.2. Dietary Restrictions

Subjects must refrain from excessive consumption of alcohol (ie, no more than 2 alcoholic beverages daily) or more than 7 alcoholic beverages weekly within 7 days of baseline (Day -1) and not consume any alcohol within 48 hours of baseline (Day -1). Subjects must refrain from

excessive consumption of alcohol (ie, no more than 2 alcoholic beverages daily) during the remainder of the study. Subjects should not consume alcohol within 24 hours of their visits at Week 4, Week 6 (Day 2), or Week 7 (Day 2).

9.9.3. Other Restrictions

Subjects must not donate blood within 30 days or donate plasma within 7 days of baseline (Day -1) and until 30 days after the final study visit or early termination. Male subjects must agree to refrain from donating sperm for 90 days after the last dose of study drug. Subjects must continue using contraception for 30 days after the last dose of study drug for females and 90 days after the last dose of study drug for males.

Participation in another investigational drug study is prohibited 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

9.10.1. Reasons for Withdrawal

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 (cardiologist verified) 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 for other reasons as described below. These should be discussed on a case-by-case basis with the NBI Medical Monitor (or designee) prior to withdrawing the subject from the study.

- Develops a clinically significant laboratory (eg, ALT or AST ≥2.5 times ULN) or ECG abnormality.
- Requires a medication that is prohibited by the protocol.

All subjects prematurely discontinuing the study, regardless of cause, should be encouraged to have all early termination assessments performed.

9.10.2. 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 will be asked to 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.

9.10.3. 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

10.1.1. Valbenazine

Valbenazine will be supplied as capsules containing 20 or 40 mg of valbenazine (free base equivalent as the ditosylate salt). The doses that will be used in this study are: 40 mg once daily taken as two valbenazine 20 mg capsules and 80 mg once daily taken as two valbenazine 40 mg capsules. Subjects randomized to receive valbenazine will receive 40 mg for the first week and 80 mg for the remainder of their valbenazine treatment.

10.1.2. Placebo

Placebo capsules identical in appearance to valbenazine capsules will be used in this study. Subjects randomized to placebo will take 2 placebo capsules daily on an identical schedule as subjects randomized to valbenazine for the first 4 weeks of the study. All subjects will take 2 placebo capsules daily for the last 3 weeks of the study.

10.2. Study Drug Storage

Study drug 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 rules. 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 7 days of dosing plus 3 extra dose days or 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 7-week, randomized, double-blind, placebo-controlled treatment period during which the subject, investigator, all study center personnel, and the Sponsor will be blinded to the subject's treatment. An IWRS will be used to maintain the study blind. Although all subjects will receive placebo for the final 3 weeks of the study, investigators, study center personnel, and the Sponsor will remain blinded to subjects' initial treatment. Additionally, subjects will not be informed that they will receive placebo for the final 3 weeks of the study, and the study design will be explained to subjects in manner that this information is not revealed.

The randomization code will be broken for an individual subject only 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 11.4.3 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 Preparation and Administration

Study drug will be administered once daily at home and the capsules must be swallowed with at least 250 mL of water, with or without food, each morning at approximately the same time (between 0700 and 1000 hours). 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. Study Drug Compliance and Accountability

Subjects will bring all unused study drug and empty drug packaging material to the center at specified study visits for drug accountability and reconciliation by study center personnel. A compliance check will be performed by counting the capsules returned at each study visit. A representative from the study center will call the subjects at the end of Weeks 2 and 3 to remind them to take their study drug daily.

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 on the study drug return form.

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 has signed the ICF until the subject's final study visit (or upon 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.

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.

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.

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.
- Treatment failure or lack of efficacy.
- Pregnancy

11.1.1. 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 adverse event 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 adverse event 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 adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

11.1.2. 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.

11.2. Recording Adverse Events

For randomized subjects, each AE will be listed as a separate entry on an AE eCRF. Screen failure subjects will have AE information noted only in the source document. The investigator (or designee) will provide information on dates 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 (see Section 11.4).
- Pregnancy (see Section 11.5).
- Treatment unblinding for any reason.
- 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.

11.3. Poststudy 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 visit or at 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.

11.4. 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 final study visit, whichever is longer in duration.

11.4.1. Definition of a Serious Adverse Event

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

- 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 pre-existing 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.

11.4.2. 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/IEC, if necessary) immediately (within 24 hours) of the SAE and the outcome of the SAE.

If an investigator becomes aware of an SAE within the time of informed consent until 30 days after the last dose of study drug or final study visit, whichever is longer in duration, then the event must be documented and reported as described in Section 11.4.3.

11.4.3. Reporting Serious Adverse Events and Other Immediately Reportable Events

SAEs and other immediately reportable events (defined in Section 11.2) 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 and pregnancies must 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 and other immediately reportable events, contact DSPV:

11.4.4. Expedited Safety Reports

NBI or its representatives will submit an Expedited Safety Report for any suspected adverse reaction (as defined in Section 11.1.2) 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/IEC as soon as possible. Documentation of the submission to the IRB/IEC and receipt by the IRB/IEC (if applicable) must be retained for each safety report.

11.5. 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 in Section 8.1) until 30 days (females) or 90 days (males) after the last dose of study drug. 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 center 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 (see Section 11.4.3 for contact information), followed by fax or email of the pregnancy form to NBI DSPV. A first trimester ultrasound will be required 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 Forms

The eCRF 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 study centers at the end of the center’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 center’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 study center 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 study center (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.

13. STATISTICAL AND ANALYTICAL PLAN

13.1. Overview

Descriptive and inferential statistical methods will be used to evaluate and summarize the data from this study. The term "descriptive statistics" refers to the number of subjects (n), mean, median, SD, SEM, minimum, and maximum for continuous and ordinal categorical variables; and refers to the number and percentage of subjects for categorical variables. The term "inferential statistics" refers to hypothesis tests which will be performed to assess differences between the treatment groups for selected variables. All such hypothesis tests will be tests of the null hypothesis of no difference between the treatment groups being compared versus the 2-sided alternative hypothesis that there is a difference. A 2-sided level of significance of 0.05 will be used in this study. Unless stated otherwise, "treatment group" refers to the treatment the subject is randomly assigned to receive on Day -1.

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. The SAP may include a number of additional analyses and data summaries not described in this protocol.

13.2. Analysis Sets

13.3. Safety Analysis Set

The safety analysis set will include all subjects who are randomized to a treatment group, take at least one dose of study drug, and have any postbaseline safety data. Treatment assignment will be based on randomized treatment. The safety analysis set will be used for all summaries of safety data (e.g., AEs, clinical laboratory data) and plasma concentration data.

13.3.1. Dependence and Withdrawal Analysis Set

The dependence and withdrawal analysis set will include all subjects in the safety analysis set who enter the withdrawal period (ie, subject is dispensed study drug at Week 4). The

dependence and withdrawal analysis set will be used for summaries and analyses of clinical dependence and withdrawal symptoms data.

13.3.2. Efficacy Analysis Set

The efficacy analysis set will include all subjects who are randomized to a treatment group, take at least one dose of study drug, and have a CGI-TD-I or CGI-TD-S assessment at Week 4. Treatment assignment will be based on randomized treatment. The efficacy analysis set will be used for all summaries of efficacy data.

13.4. Sample Size Determination

The sample size for this study is consistent with typical evaluations of dependence and withdrawal.

13.5. 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.

13.6. Disposition of Subjects

A summary of subject disposition will be prepared that displays the number of subjects who were randomized, who completed through Week 4, who entered the withdrawal period, and who completed the study. The number of subjects who discontinued from the study will be displayed also by reason for discontinuation.

13.7. Important Protocol Deviations

A summary of the number and percentage of subjects with important protocol deviations by deviation category and by treatment group will be provided for all randomized subjects.

13.8. Demographics and Baseline Subject Characteristics

Demographic data, subject baseline characteristics, and medical history will be summarized with descriptive statistics.

13.9. 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 by visit.

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

13.10. Clinical Dependence and Withdrawal Data

The primary assessment of withdrawal will be the number of subjects with withdrawal-related AEs (preferred terms will be prespecified in the SAP); differences between treatment groups will be tested for statistical significance using Fisher's exact test. The secondary assessment of

withdrawal will be the percentage of subjects in each treatment group who experience an increase on the PWC-20 by 5 new symptoms of moderate or severe degree or a worsening of symptoms by 2 points during Weeks 5 to 7 compared with Week 4 (Rickels et al., 2008). Other assessments of withdrawal will be the mean worst scores per treatment group on the PWC-20 and mCSSA, which will be summarized using descriptive statistics. Additionally, the percentage of subjects in each treatment group with a PWC-20 total score of 0 to 15, 16 to 30, 31 to 45, and 46 to 60 at each timepoint (baseline [Day -1], Weeks 4, 5 [Days 1, 3, 5, and 7], 6 [Days 2, 4, and 7], 7 [Days 2 and 4], and the final study visit [Week 7 Day 7 or early termination]) will be summarized using descriptive statistics. The ESS and HAM-A data will be summarized by visit with descriptive statistics. Key assessments of clinical dependence and withdrawal will be summarized descriptively by study site.

13.11. Pharmacokinetic Data

The plasma concentrations of valbenazine and its metabolite NBI-98782 will be summarized with descriptive statistics by timepoint (Weeks 1 and 4) and the valbenazine dose (40 mg or 80 mg) received prior to that timepoint. Concentrations below the lower limit of quantification will be set equal to zero for all plasma concentration summaries.

13.12. Efficacy Data

The efficacy measures in this study include the CGI-TD-I and the CGI-TD-S. For the CGI-TD-I, descriptive statistics will be presented for each visit. For the CGI-TD-S, descriptive statistics will be presented for each visit and for the changes from baseline (Day -1) to each postbaseline visit.

13.13. 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 of unique subjects experiencing each event and percentage of subjects experiencing each event.

Summary tables will be presented including all TEAEs.

Additional summaries will be presented for TEAEs leading to study drug dose reductions, premature discontinuations from the study, SAEs, and deaths.

Clinical laboratory, vital signs, ECG, C-SSRS, BPRS, BARS, SAS, and MADRS 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.

13.14. Software

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

13.15. 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 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/IEC 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/Independent Ethics Committee

The final approved protocol and the ICF will be reviewed by the IRB/IEC at the study center. 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/IEC, as well as reports of SAEs, life-threatening problems, or death.

14.3. Protocol Adherence – 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/IEC will be notified of all amendments to the protocol. Amendments to the protocol will not be implemented until written IRB/IEC approval has been received.

14.4. Required Documents

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

- Signed copy of the protocol signature page.
- Investigator's Brochure acknowledgement page.
- Completed and signed statement of investigator (Form FDA 1572).
- Financial disclosure documentation as required.
- Curriculum vitae and current medical license of the investigator and sub-investigators.
- Letter of approval from the IRB/IEC for both protocol and consent form.
- Copy of the IRB/IEC 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 their written 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 if not having done so during the study.

14.6. Study Monitoring

Throughout the course of the study, the study monitor will make frequent contacts with the investigator. This will include 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 will 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 or its designee, and the study center 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 initials.

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 to 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 the 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

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. Washington, DC: American Psychiatric Association. 1994.

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*. Washington, DC: American Psychiatric Association. 2013.

Barnes TR. A rating scale for drug-induced akathisia. Br J Psychiatry. 1989 May;154:672-6.

Chervin RD, Aldrich MS, Pickett R, Guilleminault C. Comparison of the results of the Epworth Sleepiness Scale and the Multiple Sleep Latency Test. J Psychosom Res. 1997 Feb;42(2):145-55.

Guy W. Ed. ECDEU Assessment Manual of Psychopharmacology, revised, US Department of Health, Education, and Welfare. Pub. No. (ADM), 76-338, Rockville, MD: National Institute of Mental Health – Clinical Global Impression - Improvement, p. 217-22. 1976.

Jeste DV, Palmer BW, Appelbaum PS, Golshan S, Glorioso D, Dunn LB, et al. A new brief instrument for assessing decisional capacity for clinical research. Arch Gen Psychiatry. 2007 Aug;64(8):966-74.

Kampman KM, Volpicelli JR, McGinnis DE, Alterman AI, Weinrieb RM, D'Angelo L, et al. Reliability and validity of the Cocaine Selective Severity Assessment. Addict Behav. 1998 Jul-Aug;23(4):449-61.

Maier W, Buller R, Philipp M, Heuser I. The Hamilton Anxiety Scale: reliability, validity and sensitivity to change in anxiety and depressive disorders. J Affect Disord. 1988 Jan-Feb;14(1):61-8.

Margolese HC, Chouinard G, Kolivakis TT, Beauclair L, Miller R. Tardive dyskinesia in the era of typical and atypical antipsychotics. Part 1: pathophysiology and mechanisms of induction. Can J Psychiatry 2005 Aug;50(9):541-7.

Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry. 1979 Apr; 134:382-9.

Overall JE, Gorham DR. The Brief Psychiatric Rating Scale (BPRS). Psychological Reports. 1962;10:799-812.

Overall JE, Gorham DR. The Brief Psychiatric Rating Scale (BPRS): Recent developments in ascertainment and scaling. Psychopharmacol Bull. 1988 Jan;24:97-9.

Rickels K, Garcia-Espana F, Mandos LA, Case GW. Physician Withdrawal Checklist (PWC-20). J Clin Psychopharmacol. 2008 Aug;28(4):447-51.

Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl. 1970;212:11-9.

Williams JB, Kobak KA. Development and reliability of a structured interview guide for the Montgomery-Asberg Depression Rating Scale (SIGMA). Brit J Psychiatry. 2008 Jan;192(1):52-8.

PROTOCOL AMENDMENT SUMMARY

Study Protocol Number:	**NBI-98854-TD4001**
Current Amendment and Date:	Amendment No. 3 Final Version Date: 16 April 2019
Previous Protocol Versions:	Amendment No. 2 Final Version Date: 03 October 2018 Amendment No. 1 Final Version Date: 06 September 2018 Original Protocol Final Version Date: 17 May 2018
Protocol Title:	A Phase 4, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Potential for Clinical Dependence and Withdrawal Symptoms Associated with Valbenazine
Development Phase:	Phase 4
Sponsor:	Neurocrine Biosciences, Inc., San Diego, CA Telephone: (858) 617-7600 Facsimile: (858) 617-7705

The NBI-98854-TD4001 protocol was amended to include the following changes:

1	Removed reference to adjudication of withdrawal-related adverse events by an independent group of blinded consultants.
2	Updated the protocol to indicate that the number of subjects who entered the withdrawal period will be captured in the disposition summary table.
3	Updated the protocol to include the new analysis sets.
4	Updated the protocol to indicate that treatment-emergent adverse event tables will not include the number of events and there will not be a summary table by maximum intensity.
5	Changed to Medical Monitor to [redacted]
6	Changed Clinical Drug Safety to Drug Safety and Pharmacovigilance.