Protocol Title	A Phase 4, Single-Arm, Open-Label Study to Evaluate the Effectiveness of Valbenazine on Patient- and Clinician-Reported Outcomes in Subjects With Tardive Dyskinesia
Protocol Identifier:	NBI-98854-TD4020
Phase:	Phase 4
Sponsor:	Neurocrine Biosciences, Inc. 12780 El Camino Real San Diego, CA 92130 United States
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Serious Adverse Event Reporting	Facsimile: +1 (888) 617-7551 or +1 (858) 617-7561 Email: cds@neurocrine.com
Protocol Amendment	1.0 – 29 January 2024

PROTOCOL AMENDMENTS

Protocol/Amendments	Date
Original Protocol	05 December 2022
Amendment 1.0	29 January 2024

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATS	Adjunctive treatment of schizophrenia
BARS	Barnes Akathisia Rating Scale
β-hCG	β-human chorionic gonadotropin
BMI	Body mass index
[redacted]	[redacted]
CFR	Code of Federal Regulations
CGI-TD-C	Clinical Global Impression of Change – Tardive Dyskinesia
CGI-TD-S	Clinical Global Impression of Severity – Tardive Dyskinesia
CI	Confidence interval
CNS	Central nervous system
COVID-19	Coronavirus disease-2019
[redacted]	[redacted]
CRO	Contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	Cytochrome P450
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
EQ-5D-5L	5-level EQ-5D version
EQ-VAS	EQ-visual analogue scale
ET	Early termination
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
HD	Huntington disease

HRQOL	Health-related quality of life
ICD-10	International Statistical Classification of Diseases and Related Health Problems, Tenth Edition
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
MDD	Major depressive disorder
MDMA	3,4 methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
MINI	Mini International Neuropsychiatric Interview
[redacted]	[redacted]
NBI	Neurocrine Biosciences, Inc.
PGI-C	Patient Global Impression of Change
PK	Pharmacokinetic(s)
Q1	First quartile
Q3	Third quartile
qd	Once a day
QOL	Quality of life
QTcF	Corrected QT interval using Fridericia's formula
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Simpson-Angus Scale
SD	Standard deviation
SE	Standard error
SDS	Sheehan Disability Scale
TD	Tardive dyskinesia
TDIS	Tardive Dyskinesia Impact Scale
TEAE	Treatment-emergent adverse event
TS	Tourette syndrome
UDS	Urine drug screen
ULN	Upper limit of normal

US	United States
VMAT2	Vesicular monoamine transporter 2
WBC	White blood cell
[redacted]	[redacted]

1. SYNOPSIS

Title of study: A Phase 4, Single-Arm, Open-Label Study to Evaluate the Effectiveness of Valbenazine on Patient- and Clinician-Reported Outcomes in Subjects With Tardive Dyskinesia

Protocol number: NBI-98854-TD4020

Phase of development: 4

Study centers: This study will be conducted at approximately 30 study centers in the United States (US).

Objectives

Primary:

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

Secondary:

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

Study Design:

This is a Phase 4, single-arm, open-label study to evaluate the effectiveness of valbenazine on patient- and clinician-reported outcomes assessing health-related quality of life (HRQOL), functioning, and treatment effect in subjects with TD who are receiving valbenazine for up to 24 weeks. Approximately 60 medically stable adult subjects (≥18 years of age) with schizophrenia, schizoaffective disorder, bipolar disorder, or major depressive disorder (MDD) who have neuroleptic-induced TD of at least mild severity, and who have awareness of and are experiencing at least mild distress from their abnormal movements will be enrolled. Enrolled subjects will receive valbenazine orally once a day (qd) at 40, 60, or 80 mg as described below.

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

Screening Period

All subjects must sign an informed consent form (ICF) prior to the conduct of any study-related procedures. Subjects will be screened for eligibility for up to 4 weeks prior to Day 1 (baseline).

After informed consent has been provided, subjects will undergo screening assessments to determine eligibility as outlined in the Schedule of Assessments (Table 8). The screening visit may be conducted anytime up to 28 days prior to first dose.

The Screening Period may be extended by up to 14 days for certain unavoidable circumstances (such as the coronavirus disease-2019 [COVID-19] pandemic) with approval from Sponsor or designee.

Subjects who do not meet entry criteria during the Screening Period may be considered for rescreening 1 time with the approval of the Sponsor or designee.

Treatment Period

Subjects will return to the site on Day 1 for baseline assessments as outlined in the Schedule of Assessments (Table 8). Before the subject can begin study treatment on Day 1, the investigator must ensure that the subject continues to meet study entry criteria as specified in the study inclusion/exclusion criteria (Section 5).

Valbenazine will be administered at 40 mg (minimum allowable dose), 60 mg, or 80 mg (maximum allowable dose) qd as described in Section 6.2.1. Briefly:

- From Day 1 through Week 4, subjects will take valbenazine 40 mg qd.
- After the end of Week 4 visit through Week 16, subjects will continue to take valbenazine 40 mg qd or the dose may be adjusted to 60 or 80 mg qd. Dose adjustments may be performed based on individual treatment needs, response, and/or tolerability.
- After the end of Week 16 visit through Week 24, subjects will take valbenazine 40, 60, or 80 mg qd; the dose will be assigned by the investigator at the end of Week 16 visit based on individual treatment needs, response, and/or tolerability observed during Weeks 1 to 16. Dose adjustments are not expected from Week 17 through Week 24; however, dose decreases are permitted if needed for safety or tolerability.

Subjects who are unable to tolerate the lowest dose (40 mg qd) at any time will be discontinued from study treatment and withdrawn from the study.

Subjects will have onsite and virtual study visits at scheduled times throughout the 24-week Treatment Period as outlined in the Schedule of Assessments (Table 8); study assessments and procedures are described in Section 9.

Safety Follow-Up Period

A Safety Follow-Up Visit for each subject will be conducted 14 days after the final dose of study treatment (end of Week 26 [Visit 9]) (Table 8).

Study population:

Approximately 60 medically stable adult (≥18 years of age) subjects who:

- Have a clinical diagnosis of:
  - Schizophrenia or schizoaffective disorder with neuroleptic-induced TD, or
  - Bipolar disorder with neuroleptic-induced TD, or
  - MDD with neuroleptic-induced TD
- Have at least mild TD (defined by an Abnormal Involuntary Movement Scale [AIMS] Item 8 score of ≥2 at screening) as assessed by an onsite rater and confirmed by an external reviewer using a video recording of the subject's AIMS assessment at screening. This criterion must be reconfirmed at baseline (as assessed by the onsite AIMS rater only).
- Have at least moderate dyskinetic movements in ≥1 body area (≥3 on AIMS) or at least mild dyskinetic movements in ≥2 body areas (≥2 on AIMS) at screening, as assessed by an onsite rater and confirmed by an external reviewer using a video recording of the subject's AIMS assessment. This criterion must be reconfirmed at baseline (as assessed by the onsite AIMS rater only).
- Have awareness of and are experiencing at least mild distress from their abnormal movements as defined by an AIMS Item 10 score of ≥2 at screening.

To ensure adequate representation of patients with different background psychiatric disorders and ranges of TD severity, subjects with schizophrenia or schizoaffective disorder will not exceed 50% of the enrolled study population, and subjects with mild dyskinesia will not exceed 50% of the enrolled study population.

Duration of study treatment and study participation: The expected duration of study participation for each subject is approximately 30 weeks, including a Screening Period of up to 4 weeks, a 24-week Treatment Period, and 2-week Safety Follow-Up Period.

Investigational product, dosage, and mode of administration:

Valbenazine will be taken once daily with or without food. Valbenazine should be taken at approximately the same time each day during the study; it is recommended that subjects take valbenazine at the same time as their oral antipsychotic medication(s), if appropriate.

Valbenazine will be formulated as 40, 60, and 80 mg capsules for oral administration at the following doses:

- Day 1 through Week 4: 40 mg qd
- After the end of Week 4 visit through Week 24: 40, 60, or 80 mg qd.

The dosing schedule is summarized above; refer to Section 6.2.1 for details.

Endpoints:

Primary

- Change from baseline in the Tardive Dyskinesia Impact Scale (TDIS) total score at Week 24
- Change from baseline in the Sheehan Disability Scale (SDS) Items 1, 2, and 3 at Week 24
- Change from baseline in the EQ-visual analogue scale (EQ-VAS) score at Week 24

Secondary

- Patient Global Impression of Change (PGI-C) score at Week 24
- Change from baseline in the Clinical Global Impression of Severity – Tardive Dyskinesia (CGI-TD-S) score at Week 24
- Change from baseline in the AIMS dyskinesia total score at Week 24

[redacted]

Safety

Safety endpoints include the occurrence of adverse events (AEs), observed and changes from baseline in clinical laboratory tests (hematology and clinical chemistry), vital sign measurements (including blood pressure and pulse rate), 12-lead electrocardiogram (ECG) parameters, and scores from the Columbia-Suicide Severity Rating Scale (C-SSRS), Barnes Akathisia Rating Scale (BARS), and modified Simpson-Angus Scale (SAS).

Statistical methods:

Summary of efficacy analyses

Descriptive statistics (including both categorical variable statistics [using response categories] and continuous variable statistics [using numerical scores]) will be presented for the score or the change from baseline score, as appropriate, at the end of Weeks 4, 8, 16, and 24. Two-sided 95% confidence intervals (CIs) will be included in the descriptive statistics for changes from baseline. Descriptive

statistics (including CIs for changes from baseline) will also be presented by disease category (schizophrenia/schizoaffective disorder or MDD/bipolar disorder).

2. INTRODUCTION

2.1. Background

Tardive dyskinesia (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, TD most often develops after long-term neuroleptic drug use and often persists after discontinuation of such medications. The Diagnostic and Statistical Manual of Mental Disorders, 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.

The pathophysiology of TD is not fully understood; however, postsynaptic dopamine hypersensitivity in the striatum is the most prominent feature (Margolese et al., 2005). Dysregulation of dopaminergic systems is an integral component of several central nervous system (CNS) disorders, including other hyperkinetic movement disorders and conditions such as schizophrenia and bipolar disorder. The transporter protein vesicular monoamine transporter 2 (VMAT2) plays an important role in presynaptic dopamine release, regulating monoamine uptake from the cytoplasm to the synaptic vesicle for storage and release. The differential expression of VMAT2 in human brain (versus endocrine tissue) makes agents that selectively target VMAT2 potentially useful for the treatment of CNS disorders (Weihe and Eiden, 2000).

This study is being conducted to evaluate the potential of valbenazine to improve patient- and clinician-reported outcomes in subjects with TD.

2.2. Benefit/Risk Assessment for Valbenazine

Valbenazine (valbenazine tosylate, NBI-98854) is a selective, orally active VMAT2 inhibitor developed by Neurocrine Biosciences, Inc. (NBI). Valbenazine was approved by the United States (US) Food and Drug Administration (FDA) in April 2017 for the treatment of adults with TD under the trade name INGREZZA®. Valbenazine has also been evaluated in pediatric and adult subjects for the treatment of Tourette syndrome (TS) and is currently being evaluated for the treatment of chorea associated with Huntington disease (HD), the treatment of dyskinetic cerebral palsy (DCP), and the adjunctive treatment of schizophrenia (ATS).

Valbenazine has been on the market for over 5 years for the treatment of adults with TD. A full development program of 20 clinical studies supporting the safety and effectiveness of valbenazine for the treatment of adults with TD included 3 placebo-controlled studies of patients with TD and underlying psychiatric conditions of schizophrenia/schizoaffective disorder and mood disorder (66% and 34% of subjects, respectively, in the Phase 3 study NBI-98854-1304). The valbenazine clinical program in TD enrolled more than 2000 subjects, of which 1547 unique subjects received at least 1 dose of valbenazine. Two additional studies in patients with TD have been conducted since approval. The cumulative postmarketing exposure to valbenazine as of the cutoff date of 10 April 2022 is estimated at 67,093 unique patient exposures with 58,010 patient-years of exposure.

Clinical data from healthy individuals and subjects with TD in prior studies and in patients with TD in postmarketing experience with valbenazine indicate that the FDA-approved doses of 40, 60, and 80 mg to be used in this study are generally well tolerated.

The most common treatment-emergent adverse events (TEAEs) identified in the NBI-sponsored valbenazine clinical development program of adults with TD (in 3 placebo-controlled studies of 6-week treatment duration) reported in ≥2% of subjects and at a higher percentage in valbenazine vs placebo include somnolence (10.9%; somnolence, fatigue, sedation), anticholinergic effects (5.4%; dry mouth, constipation, disturbance in attention, vision blurred, urinary retention), and balance disorders/fall (4.1%; fall, gait disturbance, dizziness, balance disorder).

In the entire valbenazine clinical development program (NBI-sponsored completed and ongoing studies) as of 10 April 2022, treatment-emergent serious adverse events (SAEs) occurring in 3 or more valbenazine-treated subjects were schizophrenia, suicidal ideation, chronic obstructive pulmonary disease, depression, mental status changes, suicide attempt, syncope, abdominal pain, and schizoaffective disorder.

Ten deaths have been reported in ongoing or completed valbenazine studies conducted by NBI: 8 occurred in subjects taking valbenazine and 2 in subjects taking placebo. All of the deaths occurred in adults and were considered not related or unlikely related to study treatment.

No cardiovascular, laboratory, or vital sign–related safety risks have been identified. Increases in serum prolactin above normal laboratory ranges have been noted; mean changes in subjects who received placebo were considerably smaller. No increased risk of depression or suicidality has been observed.

Hypersensitivity to valbenazine or any components of INGREZZA is a contraindication. A total of 6 hypersensitivity SAEs (5 in valbenazine-treated subjects and 1 in a placebo-treated subject) have been reported in clinical studies of valbenazine, including events of hypersensitivity, angioedema, rash, and Henoch-Schönlein purpura. Of these events, 3 were assessed as related to valbenazine (hypersensitivity, angioedema, and rash). A safety evaluation of these events supported a risk of developing hypersensitivity reactions with the use of valbenazine. Hypersensitivity reactions such as allergic dermatitis, angioedema, pruritis, urticaria, and rash have also been reported in the postmarketing setting.

Valbenazine can cause somnolence and related events (including fatigue and sedation). Somnolence was the most commonly reported adverse reaction that occurred at a higher percentage in valbenazine-treated subjects compared with placebo-treated subjects in the 3 placebo-controlled studies in subjects with TD, 1 placebo-controlled study in subjects with TS, and in 1 placebo-controlled study in subjects with HD.

An exposure-response analysis of clinical data from 2 studies in healthy subjects revealed an increased QT interval corrected for heart rate using Fridericia's formula (QTc) with higher plasma concentrations of the active metabolite. In subjects taking a strong cytochrome P450 (CYP)2D6 or CYP3A4 inhibitor or in subjects who are CYP2D6 poor metabolizers, plasma concentrations of the active metabolite of valbenazine may be higher and QT prolongation clinically significant.

Parkinsonism is a known risk with VMAT inhibitors. In the placebo-controlled clinical studies of valbenazine in subjects with TD, the incidence of Parkinson-like adverse events (AEs) was 3%

in subjects treated with valbenazine and <1% in placebo-treated subjects. Postmarketing safety reports have described Parkinson-like symptoms, some of which were severe and required hospitalization.

Additional information about the known and expected benefits and risks of valbenazine is provided in the Investigator's Brochure and in the INGREZZA Prescribing Information.

3. OBJECTIVES

3.1. Primary

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

3.2. Secondary

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

4. STUDY DESIGN

4.1. Overall Study Design

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

Approximately 60 medically stable adult subjects (≥18 years of age) with schizophrenia, schizoaffective disorder, bipolar disorder, or major depressive disorder (MDD) who have neuroleptic-induced TD of at least mild severity and who have awareness of and are experiencing at least mild distress from their abnormal movements will be enrolled. To ensure adequate representation of patients with different background psychiatric disorders and ranges of TD severity, subjects with schizophrenia or schizoaffective disorder will not exceed 50% of the enrolled study population, and subjects with mild dyskinesia will not exceed 50% of the enrolled study population.

Enrolled subjects will receive valbenazine orally once a day (qd) at 40, 60, or 80 mg during the study as described in Section 6.2.1.

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

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

4.1.1. Screening Period

All subjects must sign an informed consent form (ICF) prior to the conduct of any study-related procedures. Subjects will be screened for eligibility up to 4 weeks prior to Day 1 (baseline).

After informed consent has been provided, subjects will undergo screening assessments to determine eligibility as outlined in the Schedule of Assessments (Table 8). The screening visit may be conducted anytime up to 28 days prior to first dose.

The Screening Period may be extended by up to 14 days for certain unavoidable circumstances (such as the coronavirus disease-2019 [COVID-19] pandemic) with approval from Sponsor or designee.

Subjects who do not meet entry criteria during the Screening Period may be considered for rescreening 1 time with the approval of the Sponsor or designee.

4.1.2. Treatment Period

Subjects will return to the site on Day 1 for baseline assessments as outlined in the Schedule of Assessments (Table 8). Before the subject can begin study treatment on Day 1, the investigator must ensure that the subject continues to meet study entry criteria as specified in the study inclusion/exclusion criteria (Section 5).

Valbenazine will be administered at doses(s) of 40 mg (minimum allowable dose), 60 mg, or 80 mg (maximum allowable dose) qd as described in Section 6.2.1. Briefly:

- From Day 1 through Week 4, subjects will take valbenazine 40 mg qd.
- After the end of Week 4 visit through Week 16, subjects will continue to take valbenazine 40 mg qd or the dose may be adjusted to 60 or 80 mg qd. Dose adjustments may be performed based on individual treatment needs, response, and/or tolerability.
- After the end of Week 16 visit through Week 24, subjects will take valbenazine 40, 60, or 80 mg qd; the dose will be assigned by the investigator at the end of Week 16 visit based on individual treatment needs, response, and/or tolerability observed during Weeks 1 to 16. Dose adjustments are not expected from Week 17 through Week 24; however, dose decreases are permitted if needed for safety or tolerability.

Subjects who are unable to tolerate the lowest dose (40 mg qd) at any time will be discontinued from study treatment and withdrawn from the study.

Subjects will have onsite and virtual study visits at scheduled times throughout the 24-week Treatment Period as outlined in the Schedule of Assessments (Table 8); study assessments and procedures are described in Section 9.

4.1.3. Safety Follow-Up Period

A Safety Follow-Up Visit for each subject will be conducted 14 days after the final dose of study treatment (end of Week 26 [Visit 9]) (Table 8).

4.2. Rationale for Dose Selection

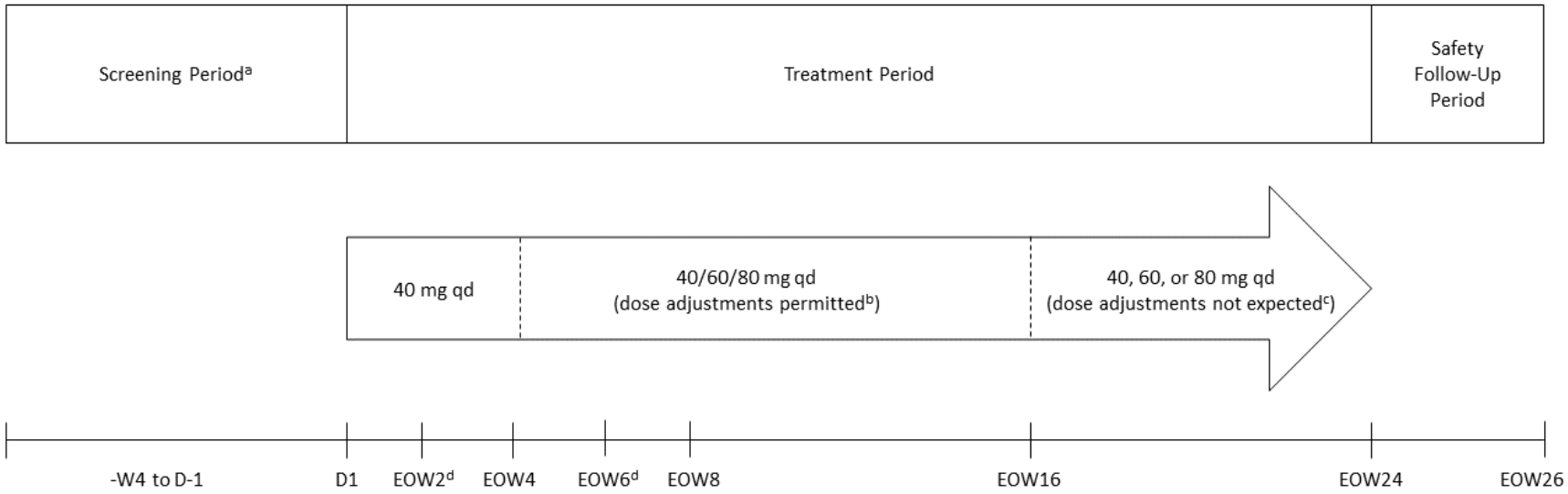
The FDA-approved INGREZZA® dose range for the treatment of adults with TD will be used in this study. The visit schedule has been selected to be consistent with a frequency commonly used in clinical practice and based on patient convenience. The dose may be adjusted (as described in Section 6.2.1) at onsite office visits.

4.3. Primary Completion and End of Study Definitions

Primary Completion: The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data used for the primary endpoints, whether the study concluded as planned or was terminated early. The planned primary completion date for this study is the date when the last subject has completed the assessments for the end of Week 24 visit. If the study is terminated early, then the primary completion date will be the date of the last visit for the last subject in the study.

End of Study: The end of study is defined as the date of the last visit shown in the Schedule of Assessments for the last subject in the study globally.

Figure 1: Study Design Schematic



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

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

[b] From the end of Week 4 visit until the end of Week 16 visit, dose adjustments may be performed based on individual treatment needs, response, and/or tolerability; refer to Section 6.2.1 for additional details.

[c] From Week 17 until the end of Week 24, dose adjustments are not expected; however, dose decreases are permitted if needed for safety or tolerability. Refer to Section 6.2.1 for additional details.

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

5. STUDY POPULATION

Subjects must fulfill all inclusion and exclusion criteria to participate in the study.

5.1. Inclusion Criteria

Subjects must meet all of the following inclusion criteria:

1. Completed informed consent.
2. At least 18 years of age.
3. Have one of the following clinical diagnoses for at least 3 months prior to screening:
    - Schizophrenia or schizoaffective disorder as defined by the DSM-5
    - Bipolar disorder as defined by the DSM-5
    - MDD as defined by the DSM-5

    This criterion will be satisfied if the clinical evaluation from the investigator supports the diagnosis and if the subject is able to meet one of the following criteria:

    - Provide a medical record of the diagnosis or confirmation by a letter from a treating physician
    - Provide a reliable self- or caregiver-reported medical history with confirmation by prescription or pharmacy records of medications taken for the disorder

    If the subject is unable to meet either of these criteria, then the investigator must confirm the psychiatric diagnosis based on an evaluation using the Mini International Neuropsychiatric Interview (MINI) using the applicable module.
4. Have a clinical diagnosis of neuroleptic-induced TD as defined by the DSM-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.
5. Have at least mild TD, defined by an Abnormal Involuntary Movement Scale (AIMS) Item 8 score of ≥2 at screening, as assessed by an onsite rater and confirmed by an external reviewer using a video recording of the subject's AIMS assessment at screening. This criterion must be reconfirmed at baseline as assessed by the onsite AIMS rater only.
6. Have at least moderate dyskinetic movements as assessed by an onsite rater and confirmed by an external reviewer using a video recording of the subject's AIMS assessment in ≥1 body area (≥3 on AIMS) or at least mild dyskinetic movements in ≥2 body areas (≥2 on AIMS) at screening. This criterion must be reconfirmed at baseline as assessed by the onsite AIMS rater only.
7. Have awareness of abnormal movements and at least mild distress associated with them as defined by an AIMS Item 10 score of ≥2 at screening and baseline.

8. Medication(s) for schizophrenia or schizoaffective disorder, bipolar disorder, or MDD and other protocol-allowed concurrent medications must meet all of the following criteria:
    - Be at a stable dose for a minimum of 30 days before Day 1:
        - No changes to the dose and frequency of ongoing medications
        - No new or discontinued medications
    - Expected to remain stable during the study

    Benzodiazepines must be at a stable dose equal to or less than the equivalent of 3 mg/day of lorazepam for 2 weeks before screening. Barbiturates and opiates must be at a stable dose for a minimum of 2 weeks before Day 1.

    This criterion will be satisfied if the investigator can confirm prior and current medications and doses through reliable subject-reported information (eg, subject provides a list of medications and doses).
9. Subjects must be outpatients and have a stable psychiatric status as clinically determined by the investigator.
10. A body mass index (BMI) of 18.0 to 42.0 kg/m^2, inclusive (BMI is defined as the subject's weight in kilograms divided by the square of the subject's height in meters).
11. Negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test at screening and urine pregnancy test on Day 1 (baseline), for females of childbearing potential.
12. Female subjects of childbearing potential must agree to use contraception consistently from screening until 30 days after the last dose of study treatment or the final study visit, whichever is longer.

    Women are considered to not be of childbearing potential if they are either postmenopausal (defined as no menses for 12 months without an alternative medical cause and confirmed by elevated follicle-stimulating hormone [FSH] consistent with a postmenopausal range) or if they have undergone permanent sterilization procedure, such as hysterectomy, bilateral salpingectomy, or bilateral oophorectomy.

    Highly effective methods of contraception are required for women of childbearing potential:

    - Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS) in place for at least 3 months before screening.
    - Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation (which may be oral, intravaginal, or transdermal) initiated and used in accordance with medical direction for at least 1 month (with no missed doses) before screening.
    - Progestogen-only hormonal contraception associated with inhibition of ovulation (which may be oral, injected, or implanted) initiated and used in accordance with medical direction at least 1 month (with no missed doses) before screening.
    - Bilateral tubal occlusion.
    - Total abstinence from sexual intercourse (periodic abstinence is not acceptable).

  - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments.
- Sexual partner(s) who had been successfully vasectomized at least 3 months prior to screening.

13. Male subjects must agree to use effective barrier contraception consistently from screening until 30 days after last dose of study treatment or final study visit, whichever is longer.

    The acceptable methods of contraception for male subjects are:

    - Condom with spermicide (cream, spray, foam, gel, suppository, or polymer film)
    - Vasectomy (successful procedure) at least 3 months prior to screening
    - Total abstinence from sexual intercourse (periodic abstinence is not acceptable)
      - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments.
14. In the opinion of the investigator, the subject is expected to complete the clinical study as designed.
15. Willing and able to comply with all study procedures and restrictions.
16. Have adequate hearing, vision, reading, and language skills to perform the procedures specified in the protocol.

5.2. Exclusion Criteria

Subjects will be excluded from the study if they meet any of the following criteria:

1. Pregnant or breastfeeding or plans to become pregnant during the study. This criterion must be reconfirmed before the first dose of study treatment on Day 1.
2. Known hypersensitivity to any component of the formulation of valbenazine.
3. Have comorbid Parkinsonism (drug-induced or otherwise) as assessed by the investigator or exhibit more than a minimal level of extrapyramidal signs/symptoms, as documented by a score on the modified Simpson-Angus Scale (SAS) (excluding Items 8 and 10) >6 at screening or Day 1 (baseline).
4. Have comorbid abnormal involuntary movement(s) (eg, Parkinsonism, akathisia) that is more prominent than TD as assessed by an external AIMS reviewer using a video recording of the subject's AIMS administration at screening.
5. Have a Barnes Akathisia Rating Scale (BARS) global clinical assessment score ≥2 at screening or Day 1 (baseline).
6. [redacted]
7. 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 Day 1 (baseline) (using Since Last Visit version) will be excluded.

8. Diagnosis of moderate or severe substance use disorder (with the exception of nicotine or caffeine dependence) within the 6 months before screening based on the MINI.
9. Positive urine drug screen (UDS) for disallowed substances, including amphetamines; cocaine; methadone; methamphetamine; MDMA; phencyclidine; or nonprescribed benzodiazepines, opiates, or barbiturates. If a subject is taking a benzodiazepine at screening, they must be on a stable dose equal to or less than the equivalent of 3 mg/day of lorazepam for 2 weeks before screening. If subject is taking prescribed barbiturates or opiates, they must be at a stable dose for a minimum of 2 weeks before Day 1.

   Note: Subjects testing positive for cannabinoids at screening may be eligible for participation in the study if all of the following criteria are met:

   - The subject does not meet the diagnostic criteria for moderate or severe substance use disorder within the 6 months before screening based on the MINI (exclusion criterion #8)
   - Based on the investigator's clinical assessment, the subject's marijuana use is limited to ≤3 times per week and is not expected to interfere with their ability to adhere to study procedures
   - Marijuana is legal per local law
10. Have an active, clinically significant unstable medical condition within 1 month (30 days) prior to Day 1 (baseline) in the judgement of the investigator, or have any laboratory value outside the normal range that is considered by the investigator to be clinically significant at the screening visit.
11. Have any known history of long QT syndrome or cardiac arrhythmia, including uncontrolled bradyarrhythmia and heart failure (class IV).
12. Have a triplicate average electrocardiogram (ECG) corrected QT interval using Fridericia's formula (QTcF) of >450 msec (male subjects) or >470 msec (female subjects) or the presence of any clinically significant cardiac abnormality during the Screening Period.
13. Have a history of severe hepatic impairment or elevation of any of the following laboratory tests:

    - Serum creatinine >1.5 × the upper limit of normal (ULN)
    - Serum aspartate aminotransferase (AST) ≥3.0 × ULN
    - Serum alanine aminotransferase (ALT) ≥3.0 × ULN
    - Gamma-glutamyl transferase (GGT) ≥3.0 × ULN
    - Serum total bilirubin >2.0 × ULN. Subjects with a documented diagnosis of Gilbert syndrome are not required to meet the bilirubin criteria.

14. Any of the following laboratory abnormalities at screening:
    - Hemoglobin <10 g/dL
    - White blood cell (WBC) count $<3.0 \times 10^3/mm^3$
    - Platelet count $<100,000/mm^3$
    - Absolute neutrophil count $<1.0 \times 10^3/mm^3$
15. Have a hematologic malignancy or solid tumor diagnosed within 3 years before screening or not in remission, with the exception of localized skin cancer or carcinoma in situ of the cervix that has been excised.
16. Have any known history of neuroleptic malignant syndrome.
17. Are currently taking any of the prohibited medications listed in Section 7.1 or have received any of these medications within 30 days (unless otherwise stated in Section 7.1) before the screening visit.
18. Has previously participated in this study; has used any active investigational drug in the context of a clinical study within 30 days or 5 half-lives before screening, whichever is longer; or has participated in 3 or more clinical studies within 12 months before screening. This criterion does not pertain to participation in an investigational vaccine clinical study, which is allowed if completed more than 30 days before screening. Eligibility based on this criterion must be reconfirmed before the first dose of study treatment on Day 1.
19. Prior (within 1 month of screening) or concomitant use of any VMAT2 inhibitor (ie, valbenazine, reserpine, tetrabenazine, deutetrabenazine) or a history of intolerance to VMAT2 inhibitors.
20. In the investigator's opinion, the subject is not capable of adhering to the protocol requirements or considered unsuitable for participation (eg, the subject lacks a stable residence, is known to have difficulty complying with treatment or medical procedures, is known to provide inaccurate medical information, or is known to attempt participation in clinical studies inappropriately).

6. STUDY TREATMENT

6.1. General Information

Study treatments are summarized in Table 1.

Table 1: Study Treatments

Treatment	Active (Valbenazine)
Treatment administration	Valbenazine will be orally self-administered by subjects once per day.
Unit dose strength	40 mg, 60 mg, or 80 mg per capsule
Dose level	Day 1 through Week 4: 40 mg After the end of Week 4 visit through Week 24: 40 mg, 60 mg, or 80 mg. The dosing schedule is provided in Section 6.2.1.
Dose formulation	Valbenazine capsules
Route of administration	Oral
Sourcing	Provided centrally by Sponsor
Packaging and labeling	Bottles containing 35 doses (1 capsule per dose). Study treatment labeling will be in accordance with applicable regulatory requirements.

6.2. Study Treatment Administration

Subjects will be instructed to take 1 capsule a day with or without food. Valbenazine should be taken at approximately the same time each day during the study; it is recommended that subjects take valbenazine at the same time as their oral antipsychotic medication(s), if appropriate. If a subject forgets or is unable to take the study treatment on a given day, the subject should not take more than 1 dose within the same day and should resume normal dosing the following day.

Subjects will take their first dose of valbenazine on Day 1. The dosing schedule is summarized in Section 6.2.1.

6.2.1. Dosing Schedule

Subjects will receive valbenazine 40 mg qd for the first 4 weeks of the Treatment Period (Day 1 through Week 4).

At each onsite study visit between the end of Week 4 (Visit 4) through the end of Week 16 (Visit 7), inclusive, the investigator should escalate the subject's dose to 60 or 80 mg qd if the dose escalation criteria below are met; otherwise, the subject should continue receiving their current dose. Dose increases are only permitted at scheduled onsite study visits.

If the subject is unable to tolerate their current dose between Week 5 and the end of Week 16 visit (Visit 7), the investigator can decrease the subject's dose. At onsite visits during this same timeframe, the investigator may increase the dose again if the dose escalation criteria are met.

At the virtual (ie, telephone) study visits, the investigator will assess tolerability and adherence to determine whether an unscheduled onsite visit is needed. Unscheduled onsite visits may be used to decrease the subject's dose if needed for tolerability.

Dose escalation criteria

All of the following criteria must be met prior to dose escalation:

- The investigator or designee's assessment of the Clinical Global Impression of Severity – Tardive Dyskinesia (CGI-TD-S) is ≥3 (ie, "mildly ill", "moderately ill", "markedly ill", "severely ill", or "among the most extremely ill patients"), or if the subject remains distressed by the presence of TD.
- The safety and tolerability of the current dose permits a dose increase as determined by the investigator.
- The subject does not meet the criteria for dosage limitations outlined in Section 7.3.

After the end of Week 16 visit through Week 24, subjects will take valbenazine 40, 60, or 80 mg qd; the dose will be assigned by the investigator at the end of Week 16 visit based on individual treatment needs, response, and/or tolerability observed during Weeks 1 to 16. After the end of Week 16 visit through Week 24, it is expected that the dose will remain stable with no dosing changes. However, dose decreases are permitted if needed for safety or tolerability.

Subjects who are unable to tolerate the lowest dose (40 mg qd) at any time will be discontinued from study treatment, withdrawn from the study, and assessed as described in Section 8.2.

The dosing schedule is summarized in Table 2.

Table 2: Dosing Schedule

Study Week	D1 (Baseline)	EOW2	EOW4	EOW6	EOW8	EOW16	EOW24/ ET	EOW26/ Safety Follow-Up
Visit	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Dose (qd)	40 mg	40 mg	40, 60, or 80 mg[a]	40, 60, or 80 mg	40, 60, or 80 mg[a]	40, 60, or 80 mg[a,b]	None	None
Type of Visit	Onsite	Virtual[c]	Onsite	Virtual[c]	Onsite	Onsite	Onsite	Onsite
Dispense Study Treatment[d]	X		X		X	X		

D=study day; EOW=end of study week; ET=early termination; qd=once a day

[a] From the end of Week 4 visit to the end of Week 16 visit, dose adjustments may be performed based on individual treatment needs, response, and/or tolerability. The investigator should escalate the subject's dose up to 80 mg qd if the dose escalation criteria are met or continue with the current dose; dose increases are only permitted at scheduled onsite study visits. From Week 5 until the end of Week 16 visit, the investigator can decrease the subject's dose if the subject is unable to tolerate their current dose. At onsite visits during this same timeframe, the investigator may increase the dose again if the dose escalation criteria are met.

[b] From Week 17 to the end of Week 24, it is expected that the dose will remain stable with no dosing changes. However, dose decreases are permitted if needed for safety or tolerability.

[c] The virtual visits (ie, telephone contacts) will be used to assess tolerability and adherence to determine whether an unscheduled onsite visit is needed.
[d] After the end of Week 4, if the investigator determines that a dose decrease is needed at an unscheduled onsite visit, then the subject will return all unused study treatment and receive a bottle of valbenazine at the new dose at this visit.

6.3. Study Treatment Storage and Compliance

The designated personnel is responsible for maintaining records of the quantity and dates of all study treatment supplies received, dispensed, returned, lost, and destroyed, according to applicable regulations and study procedures. Study treatment should be stored in a locked area accessible only to the designated pharmacist or qualified personnel. A detailed description of how study treatment should be dispensed, stored, and reconstituted, and any stability changes will be provided in the Pharmacy Manual.

6.4. Study Treatment Accountability and Return

Subjects will bring all unused study treatment and empty packaging material to the center at specified study visits for study treatment accountability and reconciliation by study center personnel. If the investigator determines that a dose decrease is needed at an unscheduled onsite visit, then the subject will return all unused study treatment and receive a bottle of valbenazine at the new dose at this visit. A compliance check will be performed by counting the capsules returned at each scheduled or unscheduled study visit.

The quantity of study treatment dispensed, used, and returned will be recorded on a dispensing log or otherwise documented. The quantity of study treatment 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 treatment supplies received, dispensed, and returned.

If unused study treatment is not returned to the Sponsor or designee, alternative disposition of study treatment must be documented and follow local laws and regulations.

6.5. Blinding

This is an open-label study during which the subject/caregiver, investigator, all study center personnel, and the Sponsor or designee will be unblinded to the subject's study treatment assignment (valbenazine).

6.6. Procedures for Overdose

Any dose of study treatment administered in excess of the protocol-specified dose will be considered an overdose.

In the event of a suspected overdose, the investigator and/or treating physician should:

1. Closely monitor the subject for any AE/SAE and laboratory abnormalities and follow the AE reporting process. The study Medical Monitor (or designee) should be contacted for

AEs related to an overdose or questions regarding clinical evaluation or management related to an overdose.

2. Document the quantity of the excess dose(s) as well as the date(s) on which additional dose(s) were taken, if this information is available.

Subjects who overdose will be counseled on correct dosing and administration of study treatment, as necessary. Decisions regarding study discontinuation, dose interruptions, or dose modifications will be made by the investigator in consultation with the Medical Monitor (or designee) based on the clinical evaluation of the subject.

7. SUBJECT RESTRICTIONS

7.1. Prior and Concomitant Medications

All prescription and over-the-counter medications, dietary supplements (including vitamins), and herbal supplements taken by the subject within 30 days before screening will be recorded on the Prior and Concomitant Medications page of the electronic case report form (eCRF). All medications taken for indications of schizophrenia/schizoaffective disorder, bipolar disorder, MDD, extrapyramidal side effects, and TD within the last 2 years will also be entered on the appropriate 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 should be treated in accordance with prevailing medical practice. All medications should be on a stable treatment regimen (including no changes to the dose and frequency of ongoing medications and no discontinuation of medications) for a minimum of 30 days before Day 1. Benzodiazepines must be at a stable dose equal to or less than the equivalent of 3 mg/day of lorazepam for 2 weeks before screening. Barbiturates and opiates must be at a stable dose for a minimum of 2 weeks before Day 1.

Investigators should confirm prior and current medications and doses through reliable subject-reported information (eg, subject provides a list of medications and doses).

Prohibited medications: The medication classes listed in Table 3 are prohibited for all subjects from 30 days before the screening visit (unless otherwise stated) until the final study visit (or early termination [ET]).

Medically appropriate episodic use of opioids, benzodiazepines, or hypnotics for acute medical conditions (eg, tooth extraction, insomnia) is permitted. Otherwise, as needed use of the following medication classes is prohibited: anticholinergics, benzodiazepines, opiates, hypnotics, antipsychotics, mood stabilizers, antidepressants, tricyclic antidepressants, and strong CYP3A4 or CYP2D6 inhibitors. A list of strong CYP2D6 and CYP3A4 inhibitors is provided in Appendix D.

Table 3: Prohibited Concomitant Medications

Medication Classes	Example Medications
Antiemetics	Metoclopramide, prochlorperazine, promethazine
Botulinum toxin[a]	Botulinum toxin injections
CYP3A4 strong inducers[b]	Phenytoin, phenobarbital, rifabutin, rifampin, primidone, St. John's Wort, carbamazepine
Dopamine agonists and precursors	Ropinirole, pramipexole, carbidopa/levodopa
MAOIs	Isocarboxazid, phenelzine, selegiline, tranylcypromine
Stimulants	Amphetamine, methylphenidate, ephedrine
VMAT2 inhibitors	Deutetrabenazine, tetrabenazine, reserpine

CYP=cytochrome P450; MAOI=monoamine oxidase inhibitors; VMAT2=vesicular monoamine transporter 2
[a] Botulinum toxin injections are prohibited from 90 days prior to screening.
[b] A list of strong CYP3A4 inducers is provided in Appendix D.

Restricted concomitant medications: Benzodiazepines, opioids, and hypnotics are not permitted within 4 hours before the start of any assessment related to the primary, secondary, or other endpoints (Sections 11.4.1 to 11.4.3) on Day 1 (baseline; Visit 2) through the end of Week 24 (Visit 8) (or the ET visit).

Digoxin: Concomitant use of valbenazine with digoxin increases digoxin levels, which may increase the risk of adverse reactions. When digoxin is coadministered with valbenazine, digoxin levels should be monitored and the dosage of digoxin adjusted if necessary.

7.2. Dietary and Other Restrictions

There are no dietary restrictions.

On the day of study visits, subjects may not use marijuana or alcohol until all assessments have been completed. If a subject appears intoxicated at a study visit, efficacy assessments should not be performed that day and the site should reschedule these assessments to the next day (or within the window defined in the Schedule of Assessments (Table 8).

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

- Male subjects must agree to refrain from donating sperm during the study and for 30 days after the last dose of the study treatment.
- Not to participate in an investigational drug study for at least 30 days after the last dose of study treatment or 30 days after study completion, whichever is longer.

7.3. Dosage Limitations in Specific Populations

Subjects in the following populations will receive a maximum dose of 40 mg valbenazine throughout the study:

- Subjects with moderate hepatic impairment
- Subjects who are known CYP2D6 poor metabolizers.
  - In the situation where CYP2D6 metabolizer status cannot be determined from the study laboratory testing, management of these subjects should be discussed with the study Medical Monitor (or designee) prior to the initiation of study treatment (before Visit 2).
- Subjects who are receiving strong CYP2D6 inhibitors or strong CYP3A4 inhibitors at screening or Day 1 and expected to continue throughout the study. The investigator should discuss subject management with the Medical Monitor (or designee) for any subjects who start or stop receiving systemic strong CYP2D6 or strong CYP3A4 inhibitors during the study. A list of strong CYP2D6 and CYP3A4 inhibitors is provided in Appendix D.

8. DISCONTINUATION OF STUDY TREATMENT AND SUBJECT WITHDRAWAL

At any time during the study, subjects can discontinue study treatment or withdraw their consent to participate in the study. The investigator must discontinue study treatment or withdraw any subject from the study at their request.

Subjects who discontinue study treatment will be withdrawn from the study.

8.1. Discontinuation of Study Treatment

If a subject prematurely discontinues study treatment, the investigator will record the reason for discontinuation on the relevant eCRF.

Subjects who are unable to tolerate the lowest dose (40 mg qd) at any time will be permanently discontinued from study treatment.

Subjects permanently discontinuing study treatment should be assessed as described in Section 8.2 and then withdrawn from the study.

Reasons for discontinuation from study treatment include, but are not limited to:

- Withdrawal by subject
- Death
- Lost to follow-up
- Site termination by the Sponsor
- Study termination by the Sponsor
- AE
- Pregnancy
- Lack of efficacy
- Protocol deviation

The investigator must discontinue study treatment 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 lowest allowable dose (40 mg)
- QTcF of >500 msec (cardiologist verified) on any ECG tracing
- If the subject is confirmed to be pregnant
- Withdrawal of consent/assent for study treatment administration by 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

The investigator or Sponsor may discontinue study treatment for other reasons as described below. These should be discussed on a case-by-case basis with the Sponsor medical monitor (or designee) prior to withdrawing the subject from the study.

- Have any of the following laboratory abnormalities:
  - ALT or AST ≥5 × ULN and considered possibly or definitely treatment-related
  - GGT ≥3.0 × ULN
  - Serum total bilirubin >2.0 × ULN
  - Serum creatinine value >1.5 × ULN
- Requires a medication that is prohibited by the protocol
- Is noncompliant with the dosing regimen (<80% dosing compliance) as verified by study treatment accountability (ie, counting the capsules returned at each study visit)

Every effort should be taken to obtain follow-up data for any subject who discontinues study treatment because of an AE, abnormal laboratory test, vital sign measurement, physical examination, or ECG finding.

8.2. Withdrawal from Study

Subjects who discontinue study treatment will be withdrawn from the study.

If a subject prematurely withdraws from the study, 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 ET assessments performed and, unless consent has been withdrawn, will be asked to come back approximately 2 weeks after their last dose for a follow-up visit. If a subject's last dose of study treatment was >2 weeks before the ET visit, no additional visit is needed.

Reasons for withdrawal from the study include, but are not limited to:

- Withdrawal of consent by subject
- AE
- Death
- Lost to follow-up
- Site terminated by Sponsor
- Study terminated by Sponsor
- Protocol deviation
- Investigator decision

8.3. Sponsor's Termination or Temporary Halt of Study or Study Site

The Sponsor or designee reserves the right to close a study site, terminate, or temporarily halt the entire study, or terminate or temporarily halt the study at individual sites, at any time for any reason. If the study is prematurely terminated or temporarily halted, the Sponsor shall promptly inform the investigators, the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), the regulatory authorities, and any contract research organizations (CROs) used in the study of the reason for termination or temporary halt, as specified by the applicable regulatory requirements. The investigator shall promptly inform the subject and should assure appropriate therapy and/or follow-up.

9. STUDY ASSESSMENTS AND PROCEDURES

A schedule of assessments is provided in Table 8 (Appendix A). No study procedures should be performed until after the subject has signed the ICF. Subject-related events and activities including specific instructions, procedures, concomitant medications, dispensing of study treatment, and descriptions of AEs should be recorded in the appropriate source documents and eCRFs.

9.1. Screening Assessments

9.1.1. Mini International Neuropsychiatric Interview for Psychotic Disorders

The MINI is brief structured diagnostic interview for the major psychiatric disorders (including schizophrenia) in the revised DSM-5 and International Statistical Classification of Diseases and Related Health Problems, Tenth Edition (ICD-10) (Sheehan et al., 1998). Validation and reliability studies have been done comparing the MINI to other well-known psychiatric diagnostic interviews. The results of these studies show that the MINI has similar reliability and validity properties to these instruments, but it can be administered in a much shorter period of time and clinicians can use it after a brief training session (Sheehan et al., 1997; Lecrubier et al., 1997).

The MINI should be administered by a healthcare professional with a clinically relevant qualification (eg, psychiatrist, psychiatric nurse, or psychologist) and documented experience assessing patients with schizophrenia, schizoaffective disorder, bipolar disorder, or MDD. Raters must be trained and certified for administration of MINI.

If a subject is unable to confirm their psychiatric diagnosis (ie, schizophrenia or schizoaffective disorder, bipolar disorder, or MDD) as outlined in inclusion criterion #3, then the applicable module of the MINI will be used at screening to evaluate the presence of psychiatric disorders in order to assess the appropriateness of the subject for inclusion.

The MINI will also be used to assess the presence of moderate or severe substance use disorder as outlined in exclusion criterion #8.

9.1.2. Abnormal Involuntary Movement Scale

The severity of TD will be assessed using the AIMS rating scale (Guy, 1976a).

9.1.2.1. AIMS Individual Items

The AIMS includes a total of 12 items and takes approximately 10 minutes to complete. The score for Items 1 through 7 ranges from 0 (no dyskinesia) to 4 (severe dyskinesia) and includes facial and oral movements (Items 1 to 4), extremity movements (Items 5 to 6), and trunk movements (Item 7). Items 8, 9, and 10 rate global judgments: Items 8 (severity of abnormal movements) and 9 (incapacitation due to abnormal movements) scores range from 0 (none, normal) to 4 (severe) and Item 10 is scored based only on the subject's report of his/her awareness of abnormal movements from 0 (no awareness) to 4 (aware, severe distress). Items 11 and 12 are yes/no questions concerning problems with teeth and/or dentures.

9.1.2.2. AIMS Dyskinesia Total Score

The AIMS dyskinesia total score is defined as the sum of the scores of AIMS items 1 through 7. If any of the seven items have a missing value, the total score for that subject/visit will be set equal to missing. The AIMS dyskinesia total score can therefore range from 0 to 28, with higher scores indicating greater severity.

9.1.2.3. Administration and Scoring of the AIMS

Administration and recording of the AIMS will be performed according to standardized guidelines to reduce variability across subjects, time points, and sites.

Specific time points for collection are provided in Table 8. At each scheduled assessment, the AIMS should be the first procedure to be administered. If possible, the same person should administer the AIMS for a given subject at all time points.

The AIMS assessment will be video recorded at the screening visit only.

9.1.2.3.1. Onsite AIMS Rater

An onsite AIMS rater (ie, the study investigator or designee) will score AIMS Items 1 to 10 and complete AIMS Items 11 to 12. Every effort should be made to have the same person rate the AIMS for a given subject throughout the study.

9.1.2.3.2. External AIMS Reviewer

An external AIMS reviewer will independently review AIMS Items 1 to 8 using a video recording of the AIMS assessment at screening. This assessment will be performed to confirm the TD severity required for study entry as outlined in inclusion criteria #5 and #6. Although the onsite rater will score the AIMS at screening, only the external AIMS reviewer's assessment will be used to determine study eligibility with respect to inclusion criteria #5 and #6.

The reviewer will be blinded to all other information about the subject.

9.1.3. CYP2D6 Genotyping

Blood samples for analysis of CYP2D6 metabolizer status (ie, poor, intermediate, normal, or ultrarapid metabolizer) will be collected during screening (Table 8). The CYP2D6 genotype status will be used to inform the pharmacokinetic (PK) assessment results but will not inform study participation. Management of subjects identified as CYP2D6 poor metabolizers and those who CYP2D6 metabolizer status cannot be determined are discussed in Section 7.3.

9.2. Efficacy Assessments

9.2.1. Tardive Dyskinesia Impact Scale

The Tardive Dyskinesia Impact Scale (TDIS) is a disease specific patient-reported outcome under development by NBI that assesses the impact of impairment and disability associated with dyskinesia (Stull et al., 2021a; Stull et al., 2021b; data on file). It defines impact of TD in terms of 6 dimensions: Mouth/Throat Function (3 items), Dexterity (2 items), Mobility (2 items), Emotional (2 items), Pain (1 item), and Social (1 item). Each item measures the impact of

dyskinetic movements in terms of difficulty or frequency over the last 7 days on a 5-point scale, with scores ranging from 0 to 4. Response options for the difficulty items range from not at all (0) to extremely (4); those for the frequency items range from never (0) to all of the time (4). The TDIS total score is the sum of the scores of TDIS Items 1 to 11. Scores can range from 0 to 44, with higher scores representing greater TD impact.

Specific time points for collection are provided in Table 8.

9.2.2. Sheehan Disability Scale

The Sheehan Disability Scale (SDS) is a brief, validated, patient-reported measure of functional impairment in a number of psychiatric disorders to measure the effect of treatment on disability (Leon et al., 1997). It includes 3 self-rated items designed to measure how work, social life, and family life are impaired by current psychiatric symptoms. Each item includes an 11-point analog scale that uses visual-spatial, numeric, and verbal descriptive anchors to represent the degree of disruption from 0 (none at all) to 10 (extremely). It also assesses the number of days a subject was unable to work/attend school and the number of days a subject was underproductive in the past week.

The SDS total score is the sum of the 3 impairment items and will only be calculated for subjects who rate all 3 items.

Specific time points for collection are provided in Table 8.

9.2.3. EQ-5D-5L and EQ-VAS

The 5-level EQ-5D version (EQ-5D-5L) is a general, single index, validated patient-reported measure for describing and valuing health (Herdman et al., 2011). It defines health in terms of 5 dimensions: Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The subject indicates his/her health state by checking the box next to the most appropriate statement. The scores for the 5 dimensions can be combined into a 5-digit number that describes the patient's health state. Subjects also rate their overall health on a 0 to 100 hash-marked, vertical EQ-visual analogue scale (EQ-VAS). The endpoints are labeled 'The best health you can imagine' and 'The worst health you can imagine.'

Specific time points for collection are provided in Table 8.

9.2.4. Patient Global Impression of Change

In the Patient Global Impression of Change-Tardive Dyskinesia (PGI-C), subjects will rate the change in their TD symptoms from the initiation of study treatment dosing by choosing one of 7 responses (very much improved, much improved, minimally improved, not changed, minimally worse, much worse, and very much worse).

Specific time points for collection are provided in Table 8.

9.2.5. Clinical Global Impression of Change - Tardive Dyskinesia

The Clinical Global Impression of Change – Tardive Dyskinesia (CGI-TD-C), which is based on a 7-point scale (range: 1=very much improved to 7=very much worse), will be used to rate the

overall global change in TD since the initiation of study treatment dosing. This scale is an adaptation of a scale developed by the Psychopharmacology Research Branch of the National Institute of Mental Health to rate the subject's overall improvement in clinical disorder and provides a global evaluation of change over time from the clinician's perspective (Guy, 1976b).

The investigator or qualified clinician designee (eg, psychologist or social worker) will rate the scale at the scheduled time points. If possible, the same person should rate the CGI-TD-C at all visits.

Specific time points for collection are provided in Table 8.

9.2.6. Clinical Global Impression of Severity - Tardive Dyskinesia

The 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, 1976b). 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 investigator or designee's assessment of the Clinical Global Impression of Severity – Tardive Dyskinesia (CGI-TD-S) is ≥3 (ie, "mildly ill", "moderately ill", "markedly ill", "severely ill", or "among the most extremely ill patients"), or if the subject remains distressed by the presence of TD.

Specific time points for collection are provided in Table 8.

9.2.7. [redacted]

[redacted]

9.2.8. [redacted]

[redacted]

[redacted]

9.2.9. Abnormal Involuntary Movement Scale

Refer to Section 9.1.2 for details.

9.3. Safety Assessments

For any abnormal safety assessment deemed clinically significant, the investigator will perform appropriate follow-up assessments 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 study treatment-emergent suicidal behavior or clinically significant suicidal ideation.

9.3.1. Vital Sign Measurements

Vital signs will be measured for the following: systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature. Blood pressure and pulse rate 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 standing, if possible. Body temperature may be measured orally or at the forehead, ear, or rectum.

Vital sign measurements will be obtained before any scheduled blood sample collection at screening and then at the time points specified in the Schedule of Assessments (Table 8).

9.3.2. Medical History

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

9.3.3. 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. The physical examination schedule is provided in Table 8.

Height will be measured at screening only. Height and weight will be measured with subjects not wearing shoes; and weight will be measured with subjects not wearing outerwear (eg, jackets or coats).

9.3.4. Electrocardiogram

A standard 12-lead ECG will be conducted in triplicate (obtained at least 3 minutes apart and within a total time of 15 minutes) after the subject has rested supine for at least 5 minutes. The ECG parameters that will be assessed include heart rate, 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 will note if the ECG is Normal, Abnormal not Clinically Significant, or Abnormal Clinically Significant. If the ECG is Abnormal Clinically Significant, the investigator will provide a description of the abnormality recorded on the AE eCRF.

9.3.5. Clinical Laboratory Assessments

All clinical laboratory assessments will be performed by a central laboratory. 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 following clinical safety laboratory assays will be performed:

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

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

The following additional laboratory tests will be performed:

Thyroid stimulating hormone: A thyroid stimulating hormone level will be measured at screening.

Drug Screen: The UDS will test for amphetamines, barbiturates, cocaine, marijuana, methadone, methamphetamine, MDMA, phencyclidine, benzodiazepines, and opiates. The UDS will be performed at screening and may be repeated at any time at the investigator's clinical judgment The UDS will be analyzed by the central laboratory.

Prolactin: Serum prolactin samples will be shipped to a central laboratory for analysis. Prolactin results will remain blinded to investigators, subjects, CRO(s), and the Sponsor until database lock.

Pregnancy Test: Pregnancy tests will be performed throughout the study for female subjects of childbearing potential. A serum β-hCG pregnancy test will be performed at screening and a urine pregnancy test (using a urine pregnancy kit provided by the central laboratory) will be performed at the time points indicated in Table 8.

9.3.6. Barnes Akathisia Rating Scale

The 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).

Specific time points for collection are provided in Table 8. The investigator or other qualified site personnel will administer and score the BARS. If possible, the same person should administer and score this scale at all time points.

9.3.7. Modified Simpson-Angus Scale

The SAS is a clinician-administered rating scale that has been widely used to assess antipsychotic-induced parkinsonism in clinical practice and research settings (Simpson and Angus, 1970). The present study uses a modified 10-item version of the SAS (for the screening and Day 1 assessment of eligibility) in which "Leg Pendulousness" and "Head Dropping" items included in the original version have been replaced with "Head Rotation" and "Akathisia," and has been used frequently in schizophrenia clinical trials (Moore and Furberg, 2017). Each item is rated using a 5-point scale (0-4); the modified SAS scores can range from 0 to 40.

Specific time points for collection are provided in Table 8. The investigator or other qualified site personnel will administer and score the modified SAS. If possible, the same person should administer and score the scales at all time points.

9.3.8. 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 one or more screening questions will prompt additional questions that evaluate frequency and intensity of suicidal ideation and/or behavior.

Of note, the Since Last Visit version of the C-SSRS will be administered at baseline and visits throughout the study, but the lookback period will be since the last C-SSRS assessment, not since the subject's last visit.

The C-SSRS will be administered and scored by the investigator or qualified study site personnel. If possible, the same person should administer and score the scale at all time points. Specific time points for collection are provided in Table 8.

9.4. Pharmacokinetic Assessments

Blood samples for determination of plasma concentrations of valbenazine and metabolites will be collected at the time points identified in the Schedule of Assessments (Table 8) or at ET.

For each sample, approximately 2 mL of blood will be collected in tubes containing dipotassium ethylenediaminetetraacetic acid (EDTA K_2). The exact time of sampling in hours and minutes will be recorded for all PK plasma samples. A PK sample should be collected from subjects who withdraw early. 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.

9.5. Caregiver Assessments

9.5.1. [redacted]

[redacted]

9.5.2. [redacted]

[redacted]

9.6. Specific Study Period Information

A complete list of study assessments to be performed at the study site during the study periods and study visits is provided in the Schedule of Assessments (Table 8).

9.6.1. Screening Period (Week -4 to Day -1)

The ICF will be reviewed with subjects and must be signed before the start of any screening procedures.

After providing informed consent, subjects will undergo screening assessments (Table 8) that may be completed in 1 or more visits during the Screening Period of up to 4 weeks. The Screening Period may be extended by up to 14 days for certain unavoidable circumstances (such as the COVID-19 pandemic) with approval from the Sponsor or designee.

The AIMS assessment should be the first procedure to be administered and will be video recorded at the screening visit. A single onsite AIMS rater will score AIMS Items 1 to 10 and complete AIMS Items 11 to 12. An external AIMS reviewer will independently review and confirm the subject's TD severity using the video recording of the AIMS assessment at

screening; only the external AIMS reviewer's assessment will be used to determine eligibility with respect to inclusion criteria #5 and #6.

Vital signs should be collected prior to the collection of blood for clinical laboratory tests.

If applicable, the subject's caregiver should be asked to complete the optional caregiver assessments [redacted] during the Screening Period or on Day 1 and at the end of Week 24.

Eligible subjects will return to the study site on Day 1 (Visit 2) for baseline assessments.

9.6.1.1. Screen Failures and Rescreening

Subjects who do not meet entry criteria during the Screening Period may be considered for rescreening 1 time with the approval of the Sponsor or designee.

9.6.2. Study Treatment Period (Day 1 to End of Week 24)

Subjects will return to the study site on Day 1 (Visit 2) for baseline assessments. Before the subject can begin study treatment, the investigator must ensure that the subject continues to meet study entry criteria as specified in Section 5.

As described in Section 7.1, if the subject has taken any restricted concomitant medications within 4 hours of any onsite visit during the Treatment Period, then the site should delay or reschedule these study visit assessments within the window defined in the Schedule of Assessments (Table 8).

At each visit, subjects will undergo assessments as outlined in Table 8. At each scheduled onsite visit, the AIMS should be the first procedure to be administered. The remaining key efficacy assessments (TDIS, SDS, EQ-5D-5L [including the EQ-VAS], PGI-C, CGI-TD-S, CGI-TD-C, [redacted] and [redacted] should be performed before any other study procedures or assessments. Key safety assessments include evaluation of vital signs, ECGs, clinical laboratory tests, physical examination, concomitant medications, and AEs. In addition, the following safety assessments will be administered: C-SSRS (Since Last Visit version), BARS, and modified SAS. The optional caregiver assessments, as described in Section 9.5, may be administered on Day 1 and at the end of Week 24.

At each onsite study visit between the end of Week 4 (Visit 4) through the end of Week 16 (Visit 7), inclusive, the investigator should adjust the subject's dose as appropriate based on individual treatment needs, response, and/or tolerability as described in Section 6.2.1. Dose increases are only permitted at scheduled onsite study visits. No dose adjustments are permitted after the end of Week 16 visit.

At the virtual study visits, the investigator will assess tolerability and adherence to determine whether an unscheduled onsite visit is needed. If an unscheduled onsite visit is needed, the following assessments are required: vital signs (blood pressure, pulse, and temperature), concomitant medications, AE monitoring, C-SSRS Since Last Visit Version, and study treatment accountability.

9.6.3. End of Study/Follow-Up Period (Week 26)

Subjects will return to the study site 14 days after their last dose of study treatment for the Safety Follow-Up Visit (end of Week 26 [Visit 9]). Key safety assessments performed at this visit include evaluation of AEs and the C-SSRS (Table 8).

10. 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/contact (or upon ET).

10.1. Definition

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that occurs after enrollment into the study and which does not necessarily have a causal relationship with the study 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, any of the following:

- Worsening or change in nature, severity, or frequency of conditions present at the start of the study
- Subject deterioration beyond what would be expected due to the primary illness
- Intercurrent illness
- Drug interaction

All suicidal behaviors and clinically significant suicidal ideations 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 treatment, 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 treatment.

The following are not considered AEs:

- Continuous persistent disease/symptom present before study treatment administration, unless it unexpectedly progresses, or increases in severity following study treatment administration
- Study treatment failure or lack of efficacy
- Pregnancy
- Overdose of either study treatment or concomitant medication without any clinical signs or symptoms

10.1.1. Intensity of Adverse Events

Adverse events must be graded for intensity. An intensity category of mild, moderate, or severe, as defined in Table 4, 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 4: Intensity of Adverse Events

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

AE=adverse event

10.1.2. Relationship to Study Treatment

The investigator will document his/her opinion of the relationship of the AE to study treatment using the criteria outlined in Table 5. An AE is deemed associated with the use of the study treatment "if there is a reasonable possibility that the treatment caused the AE" (otherwise referred to as a suspected adverse reaction). Reasonable possibility means there is evidence to suggest a causal relationship between the study treatment and the AE (Title 21 Code of Federal Regulations [CFR] 312.32 [a]).

Table 5: Relationship of Adverse Events to Study Treatment

Relationship	Description
Definite	The AE follows a reasonable temporal sequence from administration of the study treatment, abates upon discontinuation of the study treatment, follows a known or hypothesized cause-effect relationship, and (if appropriate) reappears when the study treatment is reintroduced.
Possible	The AE follows a reasonable temporal sequence from administration of the study treatment and cannot be reasonably explained by the known characteristics of the subject's clinical state, environmental, or toxic factors, or other modes of therapy administered to the subject. There should be some evidence to support a causal relationship between the study treatment and the AE.
Unlikely	The temporal sequence between the AE and the study treatment is such that the study treatment is not likely to have any reasonable association with the AE or other plausible explanations exist for the AE (eg, disease, other drugs).

Relationship	Description
Not related	The AE does not follow a reasonable temporal sequence from administration of the study treatment, may not abate upon discontinuation of the study treatment, does not follow a known or hypothesized cause-effect relationship, and (if applicable) may not reappear when the treatment is reintroduced, furthermore, there may exist a clear alternative medical explanation (eg, underlying disease state) or association with study procedure or study conduct.

AE=adverse event

10.2. Recording Adverse Events

For enrolled subjects, each AE will be listed as a separate entry on an AE eCRF. Screen failure subjects will have AE information noted 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 treatment usage, relationship to study treatment, and outcome.

10.3. 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.

Adverse events ongoing at the final visit or at ET will be followed for as long as necessary to adequately evaluate the subject's safety or until the event stabilizes, resolves, or 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.

10.4. Serious Adverse Events

All SAEs will be recorded from the time the subject has signed the ICF until the final study visit. Investigators are not obligated to actively seek SAEs after a subject has withdrawn from or completed the study. However, if the investigator learns of any SAE, including a death, at any time after a subject has been withdrawn from or has completed the study, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor as described in Section 10.4.3.

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

10.4.2. 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.

10.4.3. Reporting Serious Adverse Events and Other Immediately Reportable Events

SAEs must be reported immediately and no later than 24 hours of knowledge of the event under any circumstances, and pregnancies must be reported within 24 hours of first knowledge of the event by study personnel to NBI Drug Safety and Pharmacovigilance (DSPV). Reports of SAEs and pregnancies must be followed by a fax or email of the SAE or Pregnancy Form (Table 6). It is important that the investigator provides his/her assessment of relationship to study treatment at the time of the initial SAE report. The investigator (or designee) will also notify the IRB/IEC, if necessary) of the SAE and the outcome of the SAE, as required by the IRB/IEC.

Additionally, the following categories of medical events that could occur during participation in a clinical study must be reported within 24 hours to the study Medical Monitor (Table 6).

- 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.

Table 6: Contact Information for Drug Safety and Pharmacovigilance and Medical Monitor

Drug Safety and Pharmacovigilance Facsimile Email	 +1 (888) 617-7551 or +1 (858) 617-7561 cds@neurocrine.com
Study Medical Monitor	+1 (973) 659-6677 or +1 (512) 652-0191

10.4.4. Expedited Safety Reports

The Sponsor or its representatives will submit an Expedited Safety Report for any suspected adverse reaction (Section 10.1.2) 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.

The Sponsor 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.

10.5. Urgent Safety Measures

If an event occurs that is related to the conduct of the study or the development of the study treatment, and this new event is likely to affect the safety of subjects, the Sponsor and the investigator will take appropriate urgent safety measures to protect subjects against any immediate hazard. The Sponsor will work with the investigator to ensure the IRB/IEC and local regulatory authority is notified within 3 days or in accordance with applicable local laws and regulations.

10.6. Pregnancy

Pregnancy is neither an AE nor an SAE unless the criteria for an SAE are met. However, all pregnancies in subjects who received valbenazine will be followed to assess for pregnancy outcome. Subjects of childbearing potential must be counseled at all visits to continue using contraception until 30 days after the last dose of study treatment or final study visit, whichever is longer (inclusion criteria #12 and #13, Section 5.1). If a female subject believes she is pregnant at any time between signing the ICF and the last study visit, she should return to the study center within 24 hours and undergo a serum pregnancy test. Female subjects confirmed to be pregnant will be discontinued from the study treatment and withdrawn from the study.

All confirmed pregnancies in female subjects or in female partners of male subjects who received study treatment must be immediately reported to NBI (contact information is provided in Section 10.4.3), followed by fax or email of the pregnancy form to NBI DSPV. A first trimester ultrasound may be requested for all confirmed pregnancies. Pregnancies in subjects

who received valbenazine will be followed until resolution (ie, termination [voluntary or spontaneous] or birth).

Male subjects with female partners who become pregnant during the study must notify the study center as soon as possible. The study center will ask to follow the subject's partner's pregnancy.

11. STATISTICAL METHODS

This section represents a brief description of the planned primary analysis of the primary and secondary objectives. A comprehensive and detailed statistical analysis plan (SAP) will be generated and finalized prior to study database lock. The SAP will provide additional details regarding the methods of analysis summarized in this protocol, will describe analysis methods for other endpoints, will describe analyses to characterize the study conduct and population, and may describe sensitivity and supplementary analyses for selected endpoints.

11.1. Statistical Hypothesis and Estimands

Not applicable because this is a single-arm estimation study.

11.2. Sample Size Determination

The sample size for this open-label, single-arm study is not based on power calculations, but on clinical and logistical considerations.

Assuming that 74% of subjects complete the Week 24 assessments, approximately 60 subjects will be enrolled to achieve a total of 44 subjects for the primary analysis.

For example, for the primary endpoint of change from baseline in TDIS at Week 24, a sample size of 44 subjects will provide a 2-sided 95% confidence interval (CI) that extends 2.5 from the observed mean, assuming that the standard deviation (SD) is known to be 8.55 and the CI is based on the large sample Z statistic. In an NBI-sponsored open-label study of subjects with neuroleptic-induced TD and either schizophrenia/schizoaffective disorder or mood disorder who received valbenazine for 48 weeks (Study NBI-98854-1402 [KINECT 4]), the change from baseline at Week 24 in TDIS ranged from -6.3 to -11.1 depending on valbenazine dose and disease category, with an SD of approximately 8.55.

11.3. Analysis Sets

Statistical analysis sets are defined in Table 7. Additional analysis sets may be specified in the SAP.

Table 7: Analysis Sets

Population	Description
Full analysis set	The full analysis set includes all enrolled subjects with relevant baseline and postbaseline data. Subjects will be analyzed regardless of adherence to study treatment administration.
Safety analysis set	The safety analysis set will include all enrolled subjects who take at least 1 dose of study treatment.

11.4. Endpoints

11.4.1. Primary

- Change from baseline in the TDIS total score at Week 24
- Change from baseline in the SDS Items 1, 2, and 3 at Week 24
- Change from baseline in the EQ-VAS score at Week 24

11.4.2. Secondary

- PGI-C score at Week 24
- Change from baseline in the CGI-TD-S score at Week 24
- Change from baseline in the AIMS dyskinesia total score at Week 24

11.4.3. [redacted]

[redacted]

11.4.4. Safety

Safety endpoints include the occurrence of AEs, observed and changes from baseline in clinical laboratory tests (hematology and clinical chemistry), vital sign measurements (including blood pressure and pulse rate), 12-lead ECG parameters, and scores from the C-SSRS, BARS, and modified SAS.

11.5. Statistical Analyses

Descriptive statistical methods will be used to summarize the data from this study. Descriptive statistics typically include the number of subjects (n), mean, SD or standard error (SE), median, first (Q1) and third (Q3) quartile, minimum, maximum, and CIs for continuous variables; and refers to the number and percentage of subjects for categorical variables.

11.5.1. Efficacy Analyses

This section is a summary of the planned statistical methods for the primary analysis of the primary and secondary endpoints. Additional details of the analyses will be described in the SAP.

11.5.1.1. Procedure to Control for Multiple Comparisons

There are no planned inferential analyses of the data.

11.5.1.2. Primary Endpoints

Descriptive statistics (including both categorical variable statistics [using response categories (to be defined in SAP)] and continuous variable statistics [using numerical scores]) will be presented for change from baseline in the TDIS total score; SDS Items 1, 2, and 3 scores; and the EQ-VAS score at the end of Weeks 4, 8, 16, and 24. Two-sided 95% CIs will be included in the descriptive statistics for changes from baseline.

Descriptive statistics (including CIs for changes from baseline) will also be presented by disease category (schizophrenia/schizoaffective disorder or MDD/bipolar disorder).

11.5.1.3. Secondary Endpoints

Descriptive statistics for the PGI-C score and change from baseline in the CGI-TD-S score and the AIMS dyskinesia total score will presented overall and by disease category (schizophrenia/schizoaffective disorder or MDD/bipolar disorder). Two-sided 95% CIs will be included in the descriptive statistics for changes from baseline.

The AIMS dyskinesia total score is defined as the sum of the scores of AIMS items 1 to 7. If any of the seven items has a missing value, the total score for that subject/visit will be set equal to missing.

11.5.2. Safety Analyses

Safety data will be analyzed using the safety analysis set. The subject incidence of treatment-emergent AEs will be tabulated for AEs, SAEs, fatal AEs, and AEs leading to discontinuation of study treatment. Descriptive statistics will be generated for additional safety data, including selected laboratory analytes, vital signs, ECG parameters, and scores from the C-SSRS, BARS, and modified SAS assessments, which will be further described in the SAP.

11.6. Interim Analyses

There is no planned interim analysis.

12. SUPPORTING DOCUMENTATION

12.1. Case Report Forms

The eCRF data for this study are being collected with an electronic data capture (EDC) system. The EDC system and the study-specific eCRFs will comply with US FDA Title 21 CFR Part 11 and the applicable laws and regulations of the country in which the study is conducted.

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 may be loaded electronically into the appropriate eCRFs. All data entered into the eCRF will be supported by source documentation. The investigator should review the eCRFs as soon as possible after the subject visit has occurred and electronically sign the eCRFs as soon as possible after the subject completes or discontinues from 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 the Sponsor (or designee). The Sponsor 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/her electronic signature on the eCRFs as evidence thereof.

Access to the EDC system will be provided 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 or uploaded to a secure location with restricted access, in order to provide the investigator with a durable record of the center's eCRF data.

All clinical work conducted under this protocol is subject to Good Clinical Practice (GCP) regulations. This includes an inspection by the Sponsor 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 the Sponsor.

12.2. Data Capture, Review, and Validation

Data entered in the EDC system will be verified against the source data by the Sponsor (or designee); the percentage of source data verification will be determined by risk assessment. Any discrepancies will be corrected online by authorized study center personnel. After data is entered into EDC, 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 the Sponsor (or designee) 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 the Sponsor.

12.3. Coding Dictionaries

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

12.4. Ethics

The Sponsor personnel and the investigators will ensure that the study is conducted in full compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) GCP guidelines, and with the laws and regulations of the country in which the study is conducted.

The investigator and/or Sponsor/CRO will submit this protocol and any related document(s) to be provided to the subject to an IRB/IEC and to the national competent (health) authority (as applicable). Approval documentation (as applicable) from both the IRB/IEC and the national competent (health) authority must be obtained before starting the study.

12.5. General Legal References

The study will be carried out according to provisions of the US CFR, the US FDA, the laws and regulations of the country in which the study is conducted, and the ICH Guidelines for GCP. All clinical work conducted under this protocol is subject to GCP regulations. This includes an inspection by the Sponsor 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 the Sponsor or its designee.

12.6. 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 the Sponsor. 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.

A list of members participating in the IRB/IEC meetings must be provided, including the names, qualifications, and functions of these members. If that is not possible, the attempts made to obtain this information along with an explanation as to why it cannot be obtained or disclosed must be documented in the study documentation.

If a member of the site study personnel was present during an IRB/IEC meeting, it must be clear that this person did not vote.

12.7. 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 the Sponsor. The IRB/IEC and local health

authorities will be notified of all amendments to the protocol in accordance with local regulations.

Modifications made to the protocol or the ICF after receipt of the approval must also be submitted as amendments by the investigator and/or Sponsor/CRO to the IRB/IEC and to the national competent (health) authority in accordance with local procedures and regulations.

12.8. Required Documents

The investigator must provide the Sponsor 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 qualifications, as applicable
- Financial disclosure documentation as required
- Curriculum vitae and current medical license of the investigator and subinvestigators
- Letter of approval from the IRB/IEC for protocol and ICF
- Copy of the IRB/IEC approved written ICF to be used
- Laboratory documents (certifications/accreditations, normal ranges) if not provided by a central laboratory

12.9. Informed Consent

Subjects must provide informed consent.

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.

12.9.1. Caregiver Consent

Caregivers will be required to sign a consent form if completing the optional caregiver assessments [redacted]

12.10. Study Monitoring

Throughout the course of the study, the study monitor will make frequent contacts with the investigator. This will include telephone calls and monitoring visits. During the monitoring 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 treatment 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.

12.11. Quality Assurance

The study will be conducted in accordance with the Sponsor's standard operating procedures designed to ensure that all procedures are in compliance with GCP and the laws and regulations of the country in which the study is conducted. Quality assurance audits may be performed at the discretion of the Sponsor.

12.12. Record Retention

Study records should be retained in compliance with federal, national, and/or local regulations of the clinical site.

The Sponsor may request these records to be retained for a longer period if required by applicable regulatory requirements or Sponsor contractual obligations. If the investigator is unable to retain the study documents for the required amount of time, the Sponsor must be informed of the individual who will be assuming this responsibility.

12.13. Confidentiality and Data Protection

The Sponsor 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. Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

All information concerning this study and which was not previously published is considered confidential information. This confidential information shall remain the sole property of the Sponsor; it shall not be disclosed to others without written consent of the Sponsor; 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 the Sponsor as deemed necessary. To allow the use of the information derived from this clinical study and to ensure compliance with the laws and regulations of the country in which the study is conducted, the investigator is obliged to provide the Sponsor with the complete test results and all data compiled in this study.

12.14. Publication and Disclosure Policy

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. Authorship will be

determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

The Sponsor will submit study results for posting on public registry(ies) as required for compliance with applicable laws and/or regulations in the region(s) where the study is being conducted. For the purposes of study results disclosure, study completion is defined as the date of the last visit or procedure for the last subject in the study globally.

13. STUDY COMMENCEMENT AND DISCONTINUATION

Upon satisfactory receipt of all required regulatory documents, the Sponsor (or designee) will arrange that all study materials 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 the study protocol, instructions for eCRF completion, AE reporting, and overall responsibilities including those for treatment 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.

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APPENDIX A. SCHEDULE OF ASSESSMENTS

Table 8: Schedule of Assessments

Procedure	Screening Period[a] (≤4 weeks)	Baseline	Treatment Period (24 weeks)						Safety Follow-Up (14 days after last dose)
Study Week (Study Day)	**W-4 to D-1**	**D1**	**EOW2 (D15)**	**EOW4 (D29)**	**EOW6 (D43)**	**EOW8 (D57)**	**EOW16 (D113)**	**EOW24 (D169)/ ET**	**EOW26 (D183)**
Visit Window	**N/A**	**N/A**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Onsite Visit	X	X		X		X	X	X	X
Virtual Visit			X		X				
Informed consent	X								
Inclusion/exclusion criteria	X	update							
Medical history[b]	X	update							
Demographics	X								
Medication history	X	update							
Concomitant medications	X	X	X	X	X	X	X	X	X
Physical examination[c]	X							X	
Vital signs (blood pressure, pulse, and body temperature)	X	X		X		X	X	X	
12-lead ECG[d]	X							X	
Pregnancy test[e]	X (s)	X (u)		X (u)		X (u)	X (u)	X (u)	X (u)
Serum prolactin	X							X	
FSH (postmenopausal women only)	X								
Clinical laboratory tests[f]	X							X	
Urine drug screen[g]	X								
Blood sample for CYP2D6 genotyping	X								
Blood sample for PK								X	
AIMS[h]	X (v)[i]	X		X		X	X	X	
CGI-TD-S[j]		X		X		X	X	X	

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

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

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

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

[b] The MINI will be used to assess the presence of moderate or severe substance use disorder as outlined in exclusion criterion #8. If a subject is unable to confirm their psychiatric diagnosis (ie, schizophrenia or schizoaffective disorder, bipolar disorder, or MDD) as outlined in inclusion criterion #3, then the applicable module of the MINI will be used at screening to evaluate the presence of psychiatric disorders in order to assess the appropriateness of the subject for inclusion.

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

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

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

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

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

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

[i] An external AIMS reviewer will assess the overall severity of dyskinesia based on a video recording of the screening visit. This assessment will be performed to confirm the TD severity required for study entry as outlined in inclusion criteria #5 and #6.

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

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

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

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

APPENDIX B. INVESTIGATOR SIGNATURE

CLINICAL STUDY TITLE: A Phase 4, Single-Arm, Open-Label Study to Evaluate the Effectiveness of Valbenazine on Patient- and Clinician-Reported Outcomes in Subjects With Tardive Dyskinesia

PROTOCOL No.: NBI-98854-TD4020

As Agreed:

_____ _____

Principal Investigator Signature Date

PRINCIPAL INVESTIGATOR:

_____

(Print Principal Investigator Name)

STUDY CENTER:

_____

(Print Study Center Name)

APPENDIX C. SPONSOR APPROVAL SIGNATURE

The undersigned has reviewed and approves the content of this document.

[redacted] Electronically signed and dated

_____ _____ _____

[redacted]
Neurocrine Biosciences, Inc.
12780 El Camino Real
San Diego, CA 92130

APPENDIX D. LIST OF STRONG CYP2D6 INHIBITORS, CYP3A4 INHIBITORS, AND CYP3A4 INDUCERS

Table 9: Strong CYP2D6 Inhibitors

Strong CYP2D6 Inhibitors
bupropion
fluoxetine
paroxetine
quinidine
terbinafine

Note: This list may not be all-inclusive. Refer to the following for the most recent list:

- US Food and Drug Administration. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. Available at: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers
- https://www.uptodate.com/contents/image?imageKey=CARD%2F76992
- https://go.drugbank.com/categories/DBCAT002701

Table 10: Strong CYP3A4 Inhibitors

Strong CYP3A4 Inhibitors
boceprevir
cobicistat
danoprevir and ritonavir[a]
elvitegravir and ritonavir[a]
grapefruit juice
indinavir and ritonavir[a]
itraconazole
ketoconazole
lopinavir and ritonavir[a]
paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)[a]
posaconazole
ritonavir[a]
saquinavir and ritonavir[a]
telaprevir
tipranavir and ritonavir[a]
telithromycin
troleandomycin
voriconazole
clarithromycin
idelalisib
nefazodone
nelfinavir

Note: This list may not be all-inclusive. Refer to the following for the most recent list:

- US Food and Drug Administration. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. Available at: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers
- https://www.uptodate.com/contents/image?imageKey=CARD%2F76992
- https://go.drugbank.com/categories/DBCAT002701

[a] Ritonavir is usually given in combination with other anti-HIV or anti-HCV drugs in clinical practice.

Table 11: Strong CYP3A4 Inducers

Strong CYP3A4 Inducers
apalutamide
carbamazepine
enzalutamide
mitotane
phenytoin
rifampin
St. John's wort
rifabutin

Note: This list may not be all-inclusive. Refer to the following for the most recent list:

- US Food and Drug Administration. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. Available at: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers
- https://www.uptodate.com/contents/image?imageKey=CARD%2F76992
- https://go.drugbank.com/categories/DBCAT002701

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Approval Task	[redacted] Clinical 08-Feb-2024 18:29:30 GMT+0000

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