CLINICAL STUDY PROTOCOL

Amendment No. 5 Final Version: 12 April 2021

[redacted]

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy, Safety, and Tolerability of Valbenazine for the Treatment of Chorea Associated with Huntington Disease

Study No.: NBI-98854-HD3005

Reference No.: IND 142043

Development Phase: 3

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

SIGNATURES:

I agree to conduct this study in accordance with the requirements of this Clinical Study Protocol and in accordance with the following:

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

CLINICAL STUDY TITLE: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy, Safety, and Tolerability of Valbenazine for the Treatment of Chorea Associated with Huntington Disease

PROTOCOL No.: NBI-98854-HD3005

As Agreed:

_____ _____

Clinical Investigator Signature Date

PRINCIPAL INVESTIGATOR:

_____

(Print Clinical Investigator Name)

CENTER:

_____

(Print Study Center Name)

Accepted for the Sponsor:

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Date

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2. SYNOPSIS

Title of study: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy, Safety, and Tolerability of Valbenazine for the Treatment of Chorea Associated with Huntington Disease

Study number: NBI-98854-HD3005

Study site(s): Approximately 55 study sites in the United States and Canada.

Primary Study Objectives:

- Evaluate the efficacy of valbenazine to reduce chorea associated with Huntington disease (HD) using the Unified Huntington's Disease Rating Scale (UHDRS) Total Maximal Chorea (TMC) score.

Secondary Study Objectives:

- Evaluate the efficacy of valbenazine to reduce chorea associated with HD using the Clinical Global Impression of Change (CGI-C), the Patient Global Impression of Change (PGI-C), and the Quality of Life in Neurological Disorders (Neuro-QoL) Upper Extremity Function Short Form and the Neuro-QoL Lower Extremity Function Short Form.
- Evaluate the safety and tolerability of valbenazine in subjects with HD.
- [redacted]

Study design: This is a Phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of valbenazine in subjects with HD. The study includes a 4-week screening period, an 8-week dose-adjustment period, a 4-week maintenance period, and a final study visit 2 weeks following the final dose of study drug. Approximately 120 adult male and female subjects with motor manifest HD and a genetic diagnosis of HD will be enrolled.

If individual in-person study visits at the study site are not possible due to Corona Virus Disease 2019 (COVID-19) related reasons (eg, subject is not able to travel to the site for safety reasons or as part of public health measures), remote visits may be conducted on a case-by-case basis at the judgment of the investigator and in consultation with the study medical monitor; once able, the subject is to return to in-person visits at the study site. Screening, baseline, and study visits at Weeks 10 and 12 must be performed at the study site; subjects who plan on entering Study NBI-98854-HD3006 the same day as Study NBI-98854-HD3005 Week 14 must have Week 14 follow-up performed at the study site.

Before subjects can provide informed consent, the investigator (or designee) must determine whether the subject has the capacity to provide consent for study participation using the University of California, San Diego Brief Assessment of Capacity to Consent (UBACC). Only subjects who are deemed to have the capacity to provide consent may sign the informed consent form (ICF). All subjects must sign an ICF prior to the conduct of any study-related procedures. Subjects will be screened for eligibility during a screening period, which will be up to 4 weeks (28 days) prior to Day -1. Screening visit must be performed at the study site. Screening assessments may be repeated during the screening period if approved by the Study Medical Monitor. A subject who has been deemed a screen failure may be rescreened if approved by the Study Medical Monitor; during rescreening, all procedures must be conducted with the exception of Cytosine Adenine Guanine repeat (provided the results are available from a prior screening period).

Eligible subjects will be randomized 1:1 to either valbenazine or placebo treatment on Day -1 (baseline). Study drug will be administered in a blinded fashion throughout the 12-week treatment period beginning on Day 1. The baseline visit must be performed at the study site. The maximum doses during each week of the treatment period are shown in the table below.

	Dose Adjustment Period				Maintenance Period
Week	1-2	3-4	5-6	7-8	9-12
Arm 1	Placebo	Placebo	Placebo	Placebo	Placebo
Arm 2[a]	Valbenazine 40 mg	Valbenazine 60 mg	Valbenazine 80 mg	Valbenazine 80 mg	Valbenazine 80 mg

[a] Doses reflect maximum daily doses during each week.

During the dose-adjustment period, the investigator will increase a subject's dose to the next dose level if, in the investigator's opinion, the subject has tolerated the study drug at the current dose. Doses will be adjusted in a blinded manner; subjects receiving placebo will undergo the dose-adjustment process but will continue to receive placebo. Dose increases are allowed at visits at the end of Weeks 2, 4, and 6. If the subject has not tolerated the current dose, the investigator may decrease the subject's dose at any time during the dose adjustment period (the 40 mg dose can be decreased to 20 mg). Doses are to be decreased 1 dose level at a time and subjects may have multiple dose decreases during the dose-adjustment period; subjects who are unable to tolerate the 20 mg dose should remain in the study but study drug dosing will be discontinued. Subjects who have had a dose decrease may re-escalate during the dose adjustment period if the investigator considers that the dose increase would be reasonably tolerated.

During the maintenance period (beginning after the Week 8 visit through the end of Week 12), the subject's dose will be maintained. If the subject cannot tolerate the maintenance dose, the investigator may reduce the subject's dose a single time by 1 dose level (unless the subject is receiving 20 mg); if the subject cannot tolerate the lower dose, he/she should remain in the study but study drug dosing will be discontinued. Study visits at Weeks 10 and 12 during the maintenance period must performed at the study site.

During the dose-adjustment and maintenance periods, the investigator may assess that a dose level is not tolerated if a subject experiences an adverse event (AE) that is (1) deemed associated with the study drug, and (2) of either moderate or severe intensity, or a serious AE.

Follow-up assessments will be conducted at the end of Week 14 (2 weeks after the last dose of the study drug). Subjects who withdraw from the study should have an early termination visit, which has the same assessments as the Week 12 visit.

If individual in-person study visits at the study site are not possible due to COVID-19 related reasons,study visits during the dose adjustment period, the early termination visit, and Week 14 follow-up visit may be performed remotely at the judgment of the investigator and in consultation with the study medical monitor.

Study drug will be self-administered (in the presence of the subject's caregiver, if applicable) once daily (qd) beginning on Day 1. Study drug should be administered at approximately the same time each day during the study. As much as possible, all study visits (including baseline and follow-up) should occur at approximately the same time to standardize the time of day for the assessment of efficacy, safety, and drug exposure. Visits during the treatment period and the follow-up visit will have a window of ±3 days.

An independent Data and Safety Monitoring Board (DSMB) will periodically review ongoing, unblinded clinical safety data to ensure the safety and well-being of the study subjects.

Study population: A total of approximately 120 male and female subjects, 18 to 75 years of age, inclusive, with genetically confirmed motor manifest HD will be enrolled. Of the approximately 120 subjects enrolled in the main study, approximately 50 subjects will be enrolled in the exploratory substudy with wearable movement sensors.

Duration of treatment and study participation: The expected duration of study participation for each subject is approximately 18 weeks, including up to 4 weeks (28 days) of screening, a 12-week treatment period, and a follow-up visit 2 weeks after the final dose of study drug.

Investigational product, dosage, and mode of administration: Valbenazine will be supplied as orally administered capsules containing 20 or 40 mg of valbenazine (free base equivalents as the ditosylate salt). Subjects must swallow the capsules with approximately 4 ounces of water or other liquid, with or without food. The table below shows the doses and capsules that will be used in the study.

Dose	Valbenazine 20 mg capsule	Valbenazine 40 mg capsule	Placebo capsule
Valbenazine 20 mg	1	--	1
Valbenazine 40 mg	2	--	--
Valbenazine 60 mg	1	1	--
Valbenazine 80 mg	--	2	--
Placebo	--	--	2

Reference therapy, dosage, and mode of administration: Matching placebo capsules are identical in appearance and will be orally administered in a double-blind manner (2 placebo capsules) on an identical schedule as valbenazine. Subjects must swallow the capsules with approximately 4 ounces of water or other liquid, with or without food.

Criteria for evaluation:

Efficacy:

- UHDRS.
  - Motor only: Total Maximal Chorea score, Total Motor Score
  - Full: Motor, Cognition, Behavior, Functional Assessment, Independence, Total Functional Capacity
  - Independent rating of chorea video recordings: TMC score
- PGI-C.
- CGI-C.
- Clinical Global Impression of Severity (CGI-S).
- Patient Global Impression of Severity (PGI-S).
- Neuro-QoL Upper Extremity Function Short Form.
- Neuro-QoL Lower Extremity Function Short Form.
- Short Form 36 Health Survey (SF-36).
- Huntington Disease Health Index (HD-HI)
- EuroQol 5 Dimensions 5 Levels (EQ-5D-5L)
- [redacted]

Pharmacokinetics:

Blood samples for plasma drug and metabolite concentration analyses will be collected during the study.

Safety:

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

- AEs.
- Clinical laboratory tests (hematology, clinical chemistry, and urinalysis).
- Prolactin
- Vital signs (including orthostatic blood pressure and pulse).
- Physical examinations.
- 12-lead electrocardiogram (ECG).
- Columbia-Suicide Severity Rating Scale (C-SSRS).
- UHDRS motor score (items for parkinsonism).
- Barnes Akathisia Rating Scale (BARS).
- Hospital Anxiety and Depression Scale (HADS).

Other Assessment:

- Anosognosia Scale (AS).

Statistical methods: The primary efficacy endpoint is the change from screening/baseline period baseline (the average of the screening and Day -1 assessments) to maintenance (the average of the Week 10 and Week 12 assessments) in the TMC based on on-site assessments. The primary analysis method for the TMC change from screening period baseline will be a mixed-effect model repeated measures (MMRM) analysis. The valbenazine arm will be compared with the placebo arm using a 2-sided test with a 5% level of significance.

Response based on the CGI-C and PGI-C scales defined as "much improved" or "very much improved" at Week 12 will be secondary efficacy endpoints. The change from baseline (Day -1) to Week 12 in the Neuro-QoL Lower Extremity Function and the Neuro-QoL Upper Extremity Function scores will also be secondary efficacy endpoints. All other efficacy endpoints will be exploratory.

Pharmacokinetic and safety data will be summarized using descriptive statistics.

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
ALT	alanine aminotransferase
AS	Anosognosia Scale
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
$AUC_{0-\infty}$	AUC from time 0 extrapolated to infinity
β-hCG	beta-human chorionic gonadotropin
BARS	Barnes Akathisia Rating Scale
BMI	body mass index
CAG	Cytosine Adenine Guanine
CFR	Code of Federal Regulations
CGI-C	Clinical Global Impression of Change
CGI-S	Clinical Global Impression of Severity
C_{max}	maximum plasma concentration
CNS	central nervous system
COVID-19	Coronavirus Disease 2019
CRS-PSP	Clinical Rating Scale for Progressive Supranuclear Palsy
C-SSRS	Columbia-Suicide Severity Rating Scale
[redacted]	[redacted]
CYP	cytochrome P450
DSMB	Data and Safety Monitoring Board
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	EuroQol 5 Dimensions 5 Levels
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HADS	Hospital Anxiety and Depression Scale
HBsAg	hepatitis B surface antigen
HCV-Ab	hepatitis C antibody
HD	Huntington disease
HD-HI	Huntington Disease Health Index
HIV-Ab	human immunodeficiency virus antibody
HSG	Huntington Study Group
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IPDs	important protocol deviations

IRB	Institutional Review Board
IWRS	interactive web response system
LS	least-squares
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effect model repeated measures
MoCA	Montreal Cognitive Assessment
NBI	Neurocrine Biosciences, Inc.
Neuro-QoL	Quality of Life in Neurological Disorders
NOAEL	no observed adverse effect level
PCR	polymerase chain reaction
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	pharmacokinetics
PM	poor metabolizer
PT	Preferred Term
qd	once daily
QTcF	corrected QT interval using Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SDQ	Swallowing Disturbance Questionnaire
SF-36	Short Form 36 Health Survey
SOC	System Organ Class
t½	apparent terminal half-life
TBZ	tetrabenazine
TD	tardive dyskinesia
TEAEs	Treatment-emergent adverse events
TESAEs	treatment-emergent serious adverse events
TFC	Total Functional Capacity
t_{max}	time to maximum plasma concentration
TMC	Total Maximal Chorea
TS	Tourette syndrome
UBACC	University of California, San Diego Brief Assessment of Capacity to Consent
UHDRS	Unified Huntington's Disease Rating Scale
ULN	upper limit of normal
US	United States
VMAT2	vesicular monoamine transporter 2
WBC	white blood cell

4. ETHICS

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

- Good Clinical Practice: Consolidated Guideline (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH; current version]).
- United States (US) Code of Federal Regulations (CFR) dealing with clinical studies (21 CFR parts 50, 54, 56, 312, and 314).
- Canada Food and Drugs Act and Regulations (FDAR) Part C, Division 5: Drugs for Clinical Trials Involving Human Subjects.
- Guidance for Clinical Trial Sponsors: Clinical Trial Applications, Effective March 2016, Health Canada Therapeutic Products Directorate, Health Products and Food Branch.

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

5. INTRODUCTION

5.1. Background

Huntington disease (HD) is a genetic progressive neurodegenerative disease characterized clinically by chorea, cognitive dysfunction, and psychiatric symptoms. Pathologically, HD is associated with brain atrophy characterized by loss of striatal medium spiny neurons and cortical pyramidal neurons. Neurochemically, alterations in dopamine function and neurotransmission is observed in HD patients, with increased dopamine neurotransmission observed with early stage HD symptoms manifesting as hyperkinetic abnormal involuntary movements. Later stage motor symptoms are primarily hypokinetic in nature (Frank, 2014; Cepeda et al., 2014).

Patients with HD typically have onset of symptoms at approximately 30 to 50 years of age. Five to 10% of cases are classified as juvenile onset, with patients becoming symptomatic before the age of 20. The average lifespan after symptom onset is 15 to 20 years (Frank, 2014; Roos, 2010).

One of the defining motor symptoms of HD is chorea, characterized as abnormal, abrupt, irregular, nonstereotyped movements (Thorley et al., 2018). As HD progresses, chorea can increase in frequency and amplitude (Carlozzi et al., 2016). Chorea is also associated with decreased quality of life (Carlozzi et al., 2016). While there is no established treatment to delay onset or progression of HD, treatment of HD-associated chorea could benefit some patients through improved quality of life (Thorley et al., 2018).

Valbenazine's pharmacological activity is primarily derived from its highly selective and potent major metabolite, [+]-α-dihydrotetrabenazine ([+]-α-HTBZ) (Grigoriadis et al., 2017). Valbenazine and [+]-α-HTBZ have relatively long half-lives of 15 to 22 hours, allowing for once daily dosing with consistent exposure to [+]-α-HTBZ, and more stable management of hyperkinetic movements.

5.2. NBI-98854

Valbenazine ([redacted], NBI-98854) is a selective, orally active VMAT2 inhibitor developed by NBI. Valbenazine was approved by the United States Food and Drug Administration (FDA) in April 2017 for the treatment of adults with tardive dyskinesia (TD), under the trade name INGREZZA®. Valbenazine is also under development for the treatment of Tourette syndrome (TS) and chorea associated with HD.

In nonclinical studies, NBI-98854 appears to cause little or no cytochrome P450 (CYP) enzyme inhibition or induction at pharmacologically relevant concentrations. NBI-98854 is a moderate inhibitor of P-glycoprotein (P-gp), but only at concentrations that could be achieved in the gastrointestinal tract, and is not an inhibitor of a panel of other drug transporters. NBI-98854 is metabolized by hydrolysis of NBI-98854 to NBI-98782 ([+]-α-HTBZ). NBI-98782 is subsequently metabolized in part by CYP2D6. NBI-98854 and NBI-98782 both have the ability to bind to and inhibit VMAT2. However, NBI-98782 is the most potent, and is believed to be responsible for the majority of the observed pharmacological activity of VMAT2 inhibition.

[redacted]

Clinical pharmacokinetic (PK) data indicate that when administered orally under fasted conditions, NBI-98854 is rapidly absorbed with a time to maximum plasma concentration (t_{max}) typically ranging from approximately 0.5 to 1.0 hours. The active metabolite NBI-98782 is formed gradually with a t_{max} of 4 to 8 hours and both NBI-98854 and NBI-98782 are eliminated with an apparent terminal half-life ($t_{½}$) of approximately 20 hours.

[redacted]

[redacted]

NBI-98854 has been administered [redacted] in Phase 1 studies. More than [redacted] healthy subjects or subjects from special populations received NBI-98854 in Phase 1 studies. More than [redacted] subjects[1] with TD have received NBI-98854 in Phase 2 or 3 studies. More than [redacted] subjects[1] with TS have received NBI-98854 in Phase 1b or 2 studies.

NBI-98854 may prolong the QT interval, although the degree of QT prolongation is not clinically significant at concentrations expected with recommended dosing (INGREZZA® prescribing information). In subjects taking a strong CYP2D6 or CYP3A4 inhibitor, or who are CYP2D6 poor metabolizers (PMs), NBI-98854 concentrations may be higher and QT prolongation clinically significant.

No cardiovascular, laboratory, or vital sign related safety signals have been identified. Increases in serum prolactin above normal laboratory ranges have been noted; mean changes in subjects who received placebo were considerably smaller. [redacted]

5.3. Study and Dose Rationale

The present study is a Phase 3, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy, safety, and tolerability of valbenazine administered once daily for the treatment of chorea in adult subjects with HD. Subjects will be randomized 1:1 to placebo or active treatment with a target dose of valbenazine 80 mg, or whichever lower dose (20, 40, or 60 mg) is tolerated. The subjects' individually tolerated target dose will be determined during an up to 8-week dose-adjustment period, followed by a 4-week maintenance period.

Clinical data from subjects in prior studies and post-marketing experience with valbenazine in subjects with TD indicate that this study's dosing range of 20 mg to 80 mg is generally well tolerated. [redacted]

[1] Not all exposures were in unique subjects. Includes subjects from completed studies (Clinical Study Report completed) and clinically complete studies (study is complete but Clinical Study Report is not yet complete).

[redacted] Valbenazine 40 mg and 80 mg are approved for the treatment of TD in adults.

6. STUDY OBJECTIVES

Primary Study Objectives:

- Evaluate the efficacy of valbenazine to reduce chorea associated with HD using the Unified Huntington's Disease Rating Scale (UHDRS) Total Maximal Chorea (TMC) score.

Secondary Study Objectives:

- Evaluate the efficacy of valbenazine to reduce chorea associated with HD using the Clinical Global Impression of Change (CGI-C), the Patient Global Impression of Change (PGI-C), and the Quality of Life in Neurological Disorders (Neuro-QoL) Upper Extremity Function Short Form and the Neuro-QoL Lower Extremity Function Short Form.
- Evaluate the safety and tolerability of valbenazine in subjects with HD.

[redacted]

7. STUDY DESIGN

This is a Phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of once-daily valbenazine in subjects with HD. The study includes a 4-week screening period, an 8-week dose-adjustment period, a 4-week maintenance period, and a final study visit 2 weeks following the final dose of study drug. Approximately 120 adult male and female subjects with motor manifest HD and a genetic diagnosis of HD will be enrolled.

If individual in-person study visits at the study site are not possible due to COVID-19 related reasons (eg, subject is not able to travel to the site for safety reasons or as part of public health measures), remote visits may be conducted on a case-by-case basis at the judgment of the investigator and in consultation with the study medical monitor; once able, the subject is to return to in-person visits at the study site (see Appendix A). Screening, baseline, and study visits at Weeks 10 and 12 must be performed at the study site; subjects who plan on entering Study NBI-98854-HD3006 the same day as Study NBI-98854-HD3005 Week 14 must have Week 14 follow-up performed at the study site.

Before subjects can provide informed consent, the investigator (or designee) must determine whether the subject has the capacity to provide consent for study participation using the University of California, San Diego Brief Assessment of Capacity to Consent (UBACC). Only subjects who are deemed to have the capacity to provide consent may sign the ICF. All subjects must sign an ICF prior to the conduct of any study-related procedures. Subjects will be screened for eligibility during a screening period, which will be up to 4 weeks (28 days) prior to Day -1. Screening assessments may be repeated during the screening period if approved by the Study Medical Monitor. A subject who has been deemed a screen failure may be rescreened if approved by the Study Medical Monitor; during rescreening, all procedures should be conducted

with the exception of Cytosine Adenine Guanine repeat (CAG; provided the results are available from a prior screening period).

Eligible subjects will be randomized 1:1 to either valbenazine or placebo on Day -1 (baseline). Study drug will be administered in a blinded fashion throughout the 12-week treatment period beginning on Day 1. The maximum doses during each week of the treatment period are shown in Table 1.

Table 1: Maximum Allowable Doses During the Study

	Dose Adjustment Period				Maintenance Period
Week	1-2	3-4	5-6	7-8	9-12
Arm 1	Placebo	Placebo	Placebo	Placebo	Placebo
Arm 2[a]	Valbenazine 40 mg	Valbenazine 60 mg	Valbenazine 80 mg	Valbenazine 80 mg	Valbenazine 80 mg

[a] Doses reflect maximum daily doses during each week.

During the dose-adjustment period, the investigator will increase a subject's dose to the next dose level if, in the investigator's opinion, the subject has tolerated the study drug at the current dose. Doses will be adjusted in a blinded manner; subjects receiving placebo will undergo the dose-adjustment process but will continue to receive placebo. Dose increases are allowed at visits at the end of Weeks 2, 4, and 6. If the subject has not tolerated the current dose, the investigator may decrease the subject's dose at any time during the dose adjustment period (the 40 mg dose can be decreased to 20 mg). Doses are to be decreased 1 dose level at a time and subjects may have multiple dose decreases during the dose-adjustment period; subjects who are unable to tolerate the 20 mg dose should remain in the study but study drug dosing will be discontinued. Subjects who have had a dose decrease may re-escalate during the dose adjustment period if the investigator considers that the dose increase would be reasonably tolerated.

During the maintenance period (beginning after the Week 8 visit through the end of Week 12), the subject's dose will be maintained. If the subject cannot tolerate the maintenance dose, the investigator may reduce the subject's dose a single time by 1 dose level (unless the subject is receiving 20 mg); if the subject cannot tolerate the lower dose, he/she should remain in the study but study drug dosing will be discontinued.

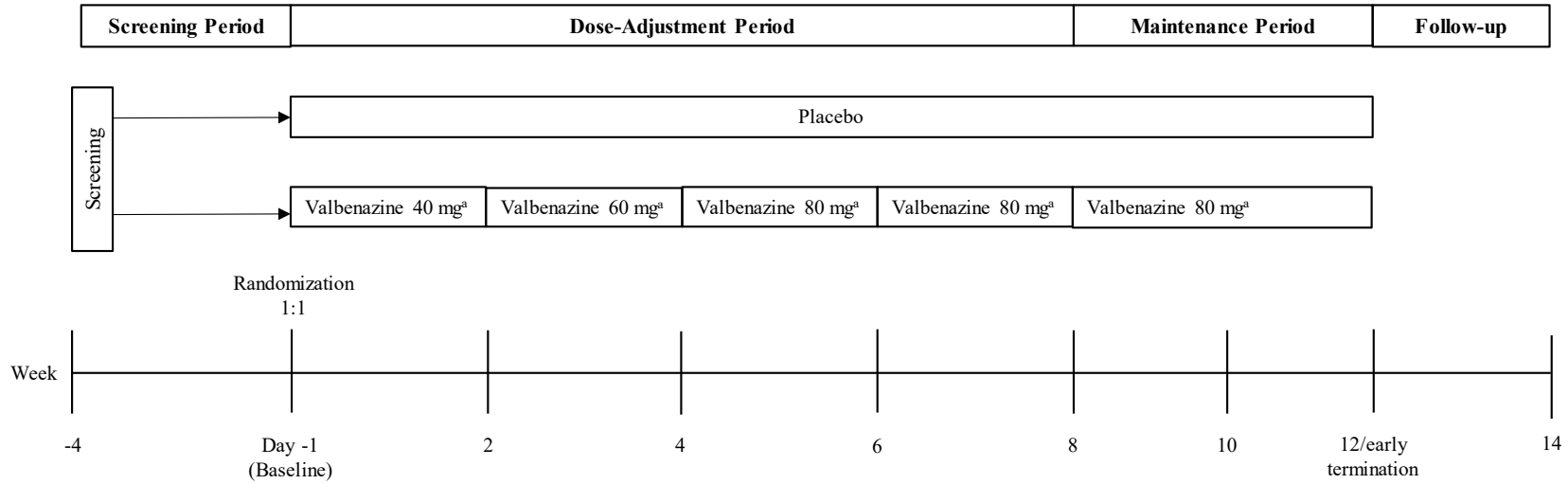
During the dose-adjustment and maintenance periods, the investigator may assess that a dose level is not tolerated if a subject experiences an adverse event (AE) that is (1) deemed associated with the study drug, and (2) of either moderate or severe intensity, or a serious AE.

Follow-up assessments will be conducted at the end of Week 14 (2 weeks after the last dose of the study drug). Subjects who withdraw from the study should have an early termination visit, which has the same assessments as the Week 12 visit.

Study drug will be self-administered (in the presence of the subject's caregiver, if applicable) once daily (qd) beginning on Day 1. Study drug should be administered at approximately the same time each day during the study. As much as possible, all study visits (including baseline and follow-up) should occur at approximately the same time to standardize the time of day for the assessment of efficacy, safety, and drug exposure. Visits during the treatment period and the follow-up visit will have a window of ±3 days.

An independent Data and Safety Monitoring Board (DSMB) will periodically review ongoing, unblinded clinical safety data to ensure the safety and well-being of the study subjects. The study design is shown in Figure 1.

Figure 1: Study Design Schematic



[a] Doses represent maximum daily doses during each 2-week period.
Early termination can happen at any time; the early termination assessments will be the same assessments as those performed at Week 12.

8. STUDY POPULATION

This study will include approximately 120 male and female subjects. Subjects must meet all inclusion criteria and no exclusion criteria in order to be enrolled.

8.1. Subject Inclusion Criteria

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

1. Be a male or female aged 18 to 75 years, inclusive.
2. Diagnosis of motor manifest HD at or before screening.
3. Genetic diagnosis of HD with an expanded CAG repeat (≥37) in huntingtin (HTT) gene at or before Day -1 (baseline).
4. Subjects must be ambulatory, but assist devices are permitted.
5. TMC score ≥8 at screening and Day -1 (baseline).
6. Total Functional Capacity (TFC) score ≥5 at screening. Subjects with a TFC score between 5 and 10 (inclusive) must have a reliable caregiver to ensure study drug administration and attendance at study visits.
7. Subjects of childbearing potential must agree to use contraception consistently while participating in the study until 30 days (females) or 90 days (males) after the last dose of the study drug. A female subject of childbearing potential is defined as a subject who is not surgically sterile (ie, bilateral oophorectomy, hysterectomy, or bilateral tubal ligation for at least 3 months prior to screening) and who has not been postmenopausal for at least 1 year prior to screening. A male subject of childbearing potential is defined as a subject who has not been vasectomized for at least 3 months prior to screening.

   Acceptable methods of contraception include the following:

   - Condom with spermicide (cream, spray, foam, gel, suppository, or polymer film).
   - Diaphragm with spermicide (with or without condom).
   - Cervical cap with spermicide (with or without condom).
   - Vaginal sponge impregnated with spermicide used with condom.
   - Intrauterine device (IUD).
   - Hormonal contraception taken for at least 3 months prior to screening.

   The following subjects are not required to use contraception:

   - Male and female subjects not of childbearing potential.
   - Subjects who practice total abstinence from sexual intercourse as the preferred lifestyle (periodic abstinence is not acceptable).
   - Female subjects with male partners not of childbearing potential.
8. Female subjects of childbearing potential must have a negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test result at screening and a negative urine pregnancy test at Day -1.

9. Have a body mass index (BMI) of 15 to 47 kg/m^2 (inclusive) at screening (BMI is defined as the subject's weight in kilograms divided by the square of the subject's height in meters).
10. Subject has voluntarily provided informed consent and has signed an ICF and is willing and able to adhere to the study regimen and study procedures described in the ICF. Subjects must also have been deemed capable of providing consent to study participation using the UBACC prior to signing the ICF.
11. Subject is able to read and understand English.
12. Be willing to provide authorization for access to personal health information in conjunction with US Health Insurance Portability and Accountability Act (HIPAA; US sites only).

[redacted]

8.2. Subject Exclusion Criteria

Subjects will be excluded from the study if they:

1. Are currently pregnant or breastfeeding.
2. Have clinically manifest dysphagia as defined by a Swallowing Disturbance Questionnaire (SDQ) score ≥11. Subjects with an SDQ score ≥11 may still be eligible per investigator judgement, if they score ≤2 on item 13 (Dysphagia) of the Clinical Rating Scale for Progressive Supranuclear Palsy (CRS-PSP).
3. Have a history or evidence of long QT syndrome, cardiac tachyarrhythmia, left bundle-branch block, atrioventricular (AV) block, uncontrolled bradyarrhythmia, or heart failure.
4. Have an average triplicate electrocardiogram (ECG) corrected QT interval using Fridericia's formula (QTcF) >450 msec (males) or >470 msec (females) or evidence of any significant cardiac abnormality at screening or Day -1 (baseline).
5. Had a medically significant illness within 30 days before Day -1 (baseline), or any history of neuroleptic malignant syndrome.
6. Have a medically significant abnormality, physical examination finding, or any other measurement or observation of clinical significance that may interfere with the objectives of the study observed during screening or Day -1 (baseline).
7. Have an unstable or serious medical or psychiatric illness at screening or Day -1 (baseline).
8. Have an untreated or undertreated psychiatric illness, such as depression. Subjects receiving antidepressant therapy may be enrolled if he/she has been on a stable dose for at least 8 weeks prior to Day -1 (baseline).
9. Have a score ≥11 on the depression subscale of the Hospital Anxiety and Depression Scale (HADS) at screening or Day -1 (baseline).
10. Have a significant risk of suicidal 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 (using Since Last Visit version) will be excluded.

11. Have a positive human immunodeficiency virus antibody (HIV-Ab) test result or hepatitis B surface antigen (HBsAg) test result at screening. Subjects with positive hepatitis C virus antibody (HCV) and confirmatory positive polymerase chain reaction (PCR) reflex test results at screening will be allowed to participate in the study provided that the subject is asymptomatic as assessed by the investigator and does not meet the liver function tests abnormalities for alanine transaminase (ALT), aspartate transaminase (AST), gamma-glutamyl transferase (GGT), and total bilirubin in exclusion criterion 12.
12. Have any of the following laboratory test abnormalities at screening:
    - Serum creatinine >1.5 times the upper limit of normal (ULN).
    - AST ≥2.5 × ULN
    - ALT ≥2.5 × ULN
    - GGT ≥3.0 × ULN
    - Total bilirubin >1.5 mg/dL
13. Have any of the following hematologic abnormalities at screening:
    - Hemoglobin <10 g/dL
    - White blood cell (WBC) count $<3.0 \times 10^3/mm^3$
    - Platelet count $<100,000/mm^3$
14. Have a positive urine drug screen at screening (positive for amphetamines, barbiturates, phencyclidine, benzodiazepines, cocaine, or opiates), except for subjects who have a prescription for benzodiazepines or opiates.
15. History of substance dependence or substance (drug) or alcohol abuse (nicotine and caffeine dependence are not exclusionary), as defined in the Diagnostic and Statistical Manual of Mental Disorders (eg, -IV or -5), within 1 year of screening.
16. Have received any prohibited medication (see Section 9.9.1).
17. Have received gene therapy at any time, or an investigational drug in the context of a clinical study within 30 days or 5 half-lives (if known), whichever is longer, of Day -1 or plan to use such investigational drug (other than the study drug) during this study.
18. Have a blood loss ≥550 mL or have donated blood within 30 days prior to Day -1 (baseline).
19. Have a history of previously established therapy with a VMAT2 inhibitor, in the judgment of the investigator and in consultation with a study medical monitor if needed. Previous exposure to a VMAT2 inhibitor is allowable provided that discontinuation occurred >30 days prior to screening, prior to establishment of a therapeutic response, and was otherwise unrelated to efficacy or tolerability.
20. [redacted]

8.3. Subject Identification and Replacement of Subjects

Subjects will be identified by their unique subject number. The subject number will be noted on electronic case report forms (eCRFs), all source documentation, laboratory documents, and ECG tracings. Subjects who discontinue from the study will not be replaced.

8.4. Randomization

The site must enter the subject's screening data in the electronic data capture (EDC) system for the Study Medical Monitor (or designee) to review, confirm eligibility, and authorize the subject to proceed to Day -1 (baseline). The investigator will review the screening and baseline eligibility criteria at Day -1 (baseline) and authorize the subject for randomization. Eligible subjects will be randomized 1:1 to either valbenazine or placebo on Day -1 (baseline) using an interactive web response system (IWRS).

9. STUDY EVALUATIONS

9.1. Schedule of Assessments

A schedule of assessments is shown in Table 2. All visits below should be performed, if possible, at the study site. Subjects will provide written informed consent before any study-related procedures are performed. Subject-related events and activities including specific instructions, procedures, concomitant medications, dispensing of study drug, and descriptions of AEs should be recorded in the appropriate source documents and eCRFs.

If individual in-person study visits at the study site are not possible due to COVID-19 related reasons (eg, subject is not able to travel to the site for safety reasons or as part of public health measures), remote visits may be conducted on a case-by-case basis at the judgment of the investigator and in consultation with the study medical monitor; once able, the subject is to return to in-person visits at the study site (see Appendix A). Screening, baseline, and study visits at Weeks 10 and 12 must be performed at the study site.

Table 2: Schedule of Assessments

Procedure[a]	Screening Period	Baseline	Dose-Adjustment Period					Maintenance Period		Follow-up
Week[b]	-4 to -1	Day -1	Day 1	2	4	6	8	10	12/ET	14[c]
Visit[b]	1	2	--	3	4	5	6	7	8	9
UBACC/informed consent[d]	X									
Treatment assignment script[e]	X	X								
Inclusion/exclusion criteria	X	update								
Medical history	X	update								
Physical examination (including weight)[f]	X	X		X	X	X	X		X	X
Height[f]	X									
Vital signs	X	X		X	X	X	X	X	X	X
12-lead ECG[g]	X	X		X	X	X	X	X	X	X
Pregnancy test[h]	X (s)	X (u)		X (u)	X (u)	X (u)	X (u)	X (u)	X (u)	X (u)
Serology (HBsAg, HCV-Ab and HIV-Ab)	X									
CAG repeat	X									
Clinical laboratory tests[i]	X	X		X	X	X	X	X	X	X
Blood sample for prolactin		X					X		X	X
Urine drug screen[j]	X									
Genotype blood sample ([redacted])[k]		X								
Blood for PK assessments[l]		X		X	X	X	X	X	X	X
HADS	X	X		X	X	X	X	X	X	X
C-SSRS	X	X		X	X	X	X	X	X	X
BARS		X		X	X	X	X	X	X	
UHDRS (full)		X							X	X
UHDRS (motor, behavior, TFC[m])	X			X	X	X	X	X		
Video recording UHDRS motor	X	X						X	X	
PGI-C and CGI-C				X	X	X	X	X	X	X
PGI-S and CGI-S		X		X	X	X	X	X	X	X
SF-36		X							X	
Neuro-QoL[n]		X			X		X	X	X	X
HD-HI		X						X	X	
EQ-5D-5L		X						X	X	
MoCA		X								
AS		X							X	X
SDQ and CRS-PSP	X									
[redacted]										
Randomization		X								
Study drug dosing			X	X	X	X	X	X	X	
Dispense study drug		X		X	X	X	X	X		
Study drug accountability[p]				X	X	X	X	X	X	
AE monitoring	X	X		X	X	X	X	X	X	X
Prior and concomitant medications	X	X		X	X	X	X	X	X	X

AE=adverse event; AS=Anosognosia Scale; BARS=Barnes Akathisia Rating Scale; CAG=Cytosine Adenine Guanine; CGI-C=Clinical Global Impression of Change; CGI-S=Clinical Global Impression of Severity; CRS-PSP=Clinical Rating Scale for Progressive Supranuclear Palsy; C-SSRS=Columbia-Suicide Severity Rating Scale; CYP=cytochrome P450; ECG=electrocardiogram; ET=early termination; EQ-5D-5L=EuroQol 5 Dimensions 5 Levels; HADS=Hospital Anxiety and Depression Scale; HBsAg=hepatitis B surface antigen; HCV-Ab=hepatitis C antibody; HD-HI=Huntington Disease Health Index; HIV-Ab=human immunodeficiency virus antibody; MoCA=Montreal Cognitive Assessment; Neuro-QoL=Quality of Life in Neurological Disorders; PGI-C=Patient Global Impression of Change; PGI-S=Patient Global Impression of Severity; PK=pharmacokinetic; QTcF=corrected QT interval using Fridericia's formula; s=serum; SDQ=Swallowing Disturbance Questionnaire; SF-36=Short Form 36 Health Survey; TFC=Total Functional Capacity; u=urine; UBACC= University of California, San Diego Brief Assessment of Capacity to Consent; UHDRS=Unified Huntington's Disease Rating Scale.

[a] As much as possible, all study visits (including baseline and follow-up) should occur at approximately the same time of day to standardize the time of day for the assessment of efficacy, safety, and drug exposure. See Section 9.7.6 for assessments to be performed during unscheduled visits.

[b] Study Visit 2 (Day -1) is the day of baseline assessments and randomization. Day 1 is the first day of dosing; study drug will be self-administered. Study visits 3 to 9 (end of Weeks 2, 4, 6, 8, 10, 12, and 14) have a visit window of ±3 days.

[c] Final study visit for subjects who complete the study; subjects who withdraw from the study should complete an early termination visit (ie, assessments listed for the Week 12 visit). Subjects may discontinue study drug dosing, but should continue participation in the study.

[d] The UBACC will be used to determine whether the subject has the capacity to provide informed consent. All subjects must provide informed consent prior to any study-related procedures.

[e] Subjects will be informed about the placebo-controlled design of the study using the treatment assignment script provided by Neurocrine Biosciences.

[f] Height and weight will be measured with subjects not wearing shoes.

[g] A standard 12-lead ECG will be conducted in triplicate (at least 1 minute apart and within approximately 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).

[h] Pregnancy tests are required for women of childbearing potential. A serum pregnancy test will be conducted at screening and urine pregnancy tests will be conducted at all subsequent visits. The urine pregnancy test result on Day -1 will be used to confirm eligibility.

[i] Clinical laboratory tests include hematology, clinical chemistry, and urinalysis. All blood samples will be obtained under non-fasted conditions.

[j] Urine drug screen will be analyzed at screening by the central lab.

[k] Blood sample for genotyping will be analyzed for randomized subjects only.

[l] Subjects will be asked to record and provide dosing times on the days during the treatment period when blood PK samples are collected.

[m] TFC will be assessed at screening only.

[n] The Neuro-QoL assessments will include both the Upper Extremity Function Short Form and the Lower Extremity Function Short Form.

[redacted]

[p] At the end of Weeks 2, 4, 6, 8, 10, and 12, subjects will return all used and unused study drug, and a compliance check will be performed by counting the capsules returned at each study visit.

9.2. Screening and Baseline Assessments

Screening and baseline visits must be performed at the study site.

9.2.1. Cytosine Adenine Guanine Repeat

A blood sample will be collected from subjects during screening to assess for CAG trinucleotide repeat expansion number in the *HTT* gene. Blood will be collected in tubes containing dipotassium ethylenediaminetetraacetic acid (EDTA K_2). Instructions for processing samples will be provided by the central laboratory. CAG repeat blood samples collected from subjects will be shipped to a central laboratory for analysis.

Prior documentation of CAG repeat ≥37 from a validated laboratory is sufficient to confirm eligibility; however, a sample will still be collected at screening for all subjects to be assessed by the central laboratory.

9.2.2. Genotyping

A blood sample will be collected from randomized subjects for the analysis of [redacted]. Blood will be collected in tubes containing EDTA K_2. Instructions for processing samples will be provided by the central laboratory. Genotyping blood samples collected from subjects will be shipped to a central laboratory for analysis.

9.2.3. Swallowing Disturbance Questionnaire

The SDQ is a 15-item instrument that assesses subjects' difficulty in swallowing food on a scale from 0 (never) to 3 (very frequently). The SDQ is a valid and reliable instrument to determine subjects' ability to swallow (Cohen and Manor, 2011). The SDQ will be administered at screening to determine eligibility for the study.

9.2.4. Clinical Rating Scale for Progressive Supranuclear Palsy

Subjects who score ≥11 on the SDQ during screening and, in the investigator's judgement, may still be eligible for participation, will be asked to complete item 13 on the CRS-PSP. Dysphagia is rated from 0 (none) to 4 (requires artificial measures) after the subject drinks 30 to 50 mL of water (Golbe and Ohman-Strickland, 2007). Subjects who score ≤2 will be eligible for the study.

9.2.5. Montreal Cognitive Assessment

The Montreal Cognitive Assessment (MoCA) is an instrument to determine cognitive abilities including: orientation, short-term memory, executive function, language abilities, abstraction, animal naming, attention, and a clock-drawing test (Nasreddine et al., 2005). The maximum score on the instrument is 30 points. The MoCA will be administered on Day -1 (baseline).

9.3. Efficacy Assessments

If individual in-person study visits at the study site are not possible due to COVID-19 related reasons (eg, subject is not able to travel to the site for safety reasons or as part of public health measures), remote visits may be conducted on a case-by-case basis at the judgment of the

investigator and in consultation with the study medical monitor; once able, the subject is to return to in-person visits at the study site (see Appendix A).

9.3.1. Unified Huntington's Disease Rating Scale

The UHDRS is a tool developed by the Huntington Study Group (HSG) to assess the clinical features and course of HD. The UHDRS has undergone extensive reliability and validity testing and has been used as a major outcome measure in controlled clinical trials (HSG, 1996). The full UHDRS includes the following assessments: motor, cognitive, behavioral, independence, function, and TFC. The motor portion of the UHDRS consists of 15 items that measure the severity of the motor symptoms.

The TMC is item 12 of the motor assessment and measures the chorea in 7 different body parts including the face, oral-buccal-lingual region, trunk and each limb independently. The maximum score is 28.

The full UHDRS will be administered Day -1 (baseline) and Weeks 12 (or early termination) and 14. The motor and behavior portions of the UHDRS will be administered at screening (including TFC), Weeks 2, 4, 6, 8, and 10. The motor only portion of the UHDRS will be video recorded at screening, Day -1 (baseline), and Weeks 10 and 12 (or early termination).

The motor and cognition portions of the UHDRS will not be administered at COVID-19 related remote visits.

9.3.1.1. Unified Huntington's Disease Rating Scale Administrator

The UHDRS will be administered and scored by the investigator (or qualified designee). If possible, the same person should administer the UHDRS for an individual subject at all timepoints.

9.3.1.2. Unified Huntington's Disease Rating Scale Video Recording

Subjects will be video recorded for the duration of the UHDRS motor section according to standardized guidelines provided by NBI (or designee). Video recordings will be uploaded to a secure, central server, and managed by a core laboratory. Access to the dedicated central server will be limited and will require the user to provide a user identification and password to access the secure server and the subject's video recording.

9.3.1.3. Blinded, Central Unified Huntington's Disease Rating Scale Motor Video Raters

The UHDRS video recording files will be reviewed and scored by blinded, central UHDRS motor video raters. A triple-blind consensus scoring will be conducted by these raters according to scoring guidelines developed by NBI. NBI (or designee) will provide the blinded central UHDRS motor video raters digital-secure access to the subjects' randomized UHDRS video recording files for review and scoring. The central raters will score maximal chorea (0 to 4) on 7 body regions (face, buccal-oral-lingual, trunk, right upper extremities, left upper extremities, right lower extremities, and left lower extremities). The central raters will be blinded to the subjects' study visits and treatment assignments. Two blinded, central raters will review each UHDRS video file from beginning to end and must agree on the TMC score. The central

UHDRS video raters will review and score the UHDRS video recordings conducted at screening, Day -1 (baseline), and Weeks 10 and 12 (or early termination).

9.3.2. Patient Global Impression of Change

Subjects will evaluate the change in their chorea symptoms since initiation of study drug dosing by choosing one of 7 responses (very much improved, much improved, minimally improved, not changed, minimally worse, much worse, and very much worse) on the PGI-C.

The PGI-C will be completed by subjects at Weeks 2, 4, 6, 8, 10, 12 (or early termination), and 14.

9.3.3. Clinical Global Impression of Change

The CGI-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 improvement of chorea since the initiation of study drug dosing. This scale is a modification 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 improvement over time from the clinician's perspective (Guy, 1976).

An investigator or qualified clinician designee (eg, psychologist or social worker) will rate the scale at the scheduled timepoints. If possible, the same person should rate the CGI-C at all timepoints. The CGI-C will be administered at Weeks 2, 4, 6, 8, 10, 12 (or early termination), and 14.

This assessment will not be conducted at COVID-19 related remote visits.

9.3.4. Patient Global Impression of Severity

The Patient Global Impression of Severity (PGI-S) scale will be used to assess overall severity of chorea on a 5-point scale (range: 1=none to 5=very severe). The PGI-S will be assessed by the subject on Day -1 (baseline) and at Weeks 2, 4, 6, 8, 10, 12 (or early termination), and 14.

9.3.5. Clinical Global Impression of Severity

The Clinical Global Impression of Severity (CGI-S) scale will be used to assess overall severity of chorea on a 7-point scale (range: 1=normal, not at all ill to 7=among the most extremely ill patient). The CGI-S will be assessed by the investigator on Day -1 (baseline) and at Weeks 2, 4, 6, 8, 10, 12 (or early termination), and 14.

This assessment will not be conducted at COVID-19 related remote visits.

9.3.6. Short Form 36 Health Survey

The SF-36 is a 36-item, self-administered questionnaire. It measures health on 8 dimensions: vitality, physical functioning, pain, general health perception, physical role limitations, emotional role functioning, social functioning, and mental health (Brazier et al., 1992). The SF-36 has been shown to be a reliable and validated instrument (Brazier et al., 1992). Version 2 of the SF-36 will be used in this study.

The SF-36 will be administered on Day -1 (baseline) and Week 12 (or early termination).

This assessment will not be conducted at a COVID-19 related remote early termination visit.

9.3.7. Quality of Life in Neurological Disorders

The Neuro-QoL is a collection of psychometrically sound, clinically relevant, health-related quality of life measurement tools for individuals with neurological conditions. The Neuro-QoL has been demonstrated to be a reliable tool for assessing patient-reported physical functioning measures in subjects with HD (Carlozzi et al., 2017). The Lower Extremity Function Short Form and the Upper Extremity Function Short Form each comprise 8 questions about physical abilities, rated from 1 (unable to do) to 5 (without any difficulty).

Both the Upper Extremity Function Short Form and the Lower Extremity Function Short Form will be administered on Day -1 (baseline), and Weeks 4, 8, 10, 12 (or early termination), and 14.

9.3.8. Huntington Disease Health Index

The Huntington Disease Health Index (HD-HI) (Glidden et al., 2017) is a disease-specific patient reported outcome measure designed to evaluate patient disease burden in therapeutic trials. The HD-HI comprises 13 subscales that measure 13 individual areas of HD patient health. Together, each of the subscales can be utilized to generate an estimate of a HD patient's overall disease burden. Each question in the instrument was selected based on its high relevance to the HD population, its ability to be consistently understood by patients and clinicians, its content validity, its face validity, and its potential responsiveness to measure therapeutic benefit of disease progression during clinical trials.

This instrument is a questionnaire that is completed by the subject (with assistance, as necessary). In standard use, the instrument is handed to a subject who is asked to read the directions and complete the instrument, using a pen, by checking the most appropriate box next to each question.

Upon completion of the HD-HI, 14 scores are generated: a subject receives a score for each of the 13 subscales and a total instrument score. The total instrument score is a composite of the 13 subscales. The score for each subscale and the total instrument ranges from 0 to 100 with 100 representing the highest disease burden and a score of 0 representing no disease burden.

The HD-HI will be administered on Day -1 (baseline) and Weeks 10 and 12 (or early termination).

This assessment will not be conducted at COVID-19 related remote visits.

9.3.9. EuroQol 5 Dimensions 5 Levels

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

number that describes the patient's health state. Subjects also rate their overall health on a 0 to 100 hash-marked, vertical visual analogue scale (EQ-VAS). The endpoints are labeled 'The best health you can imagine' and 'The worst health you can imagine.'

The EQ-5D-5L will be administered on Day -1 (baseline) and Weeks 10 and 12 (or early termination).

[redacted]

[redacted]

9.4. Pharmacokinetic Assessments

Blood samples for determination of plasma concentrations of valbenazine and the metabolite NBI-98782 will be collected on Day -1 (baseline) and Weeks 2, 4, 6, 8, 10, 12 (or early termination), and 14.

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

9.5. Safety Assessments

Concomitant medication use and AEs will be monitored throughout the study as described in Section 9.9.1 and Section 11, respectively. In the case of a COVID-19 related remote visit, concomitant medication use and AEs will still be monitored (see Appendix A). Additional safety assessments are described in the following sections.

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

Appropriate psychiatric evaluation and intervention will be provided for any treatment-emergent suicidal behavior or clinically significant suicidal ideation as determined by the clinical investigator.

9.5.1. Data and Safety Monitoring Board

An independent DSMB will periodically review ongoing, unblinded clinical data to ensure the safety and well-being of the study subjects. The data review may result in recommendation for early termination of the study or changes to the protocol and informed consent. A DSMB charter will describe the responsibilities, timing of meetings, and data review procedures for the members to follow.

9.5.2. Vital Sign Measurements

Vital sign measurements, including orthostatic systolic and diastolic blood pressure, orthostatic pulse rate, respiratory rate (recorded only supine) and oral body temperature, will be measured. 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 of standing.

Vital sign measurements will be obtained before any scheduled blood sample collection at screening, Day -1 (baseline), and Weeks 2, 4, 6, 8, 10, 12 (or early termination), and 14.

9.5.3. Medical History

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

9.5.4. Physical Examination Including Height and Weight

The complete physical examination will consist of an assessment of general appearance, skin and mucosae, head, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest/lungs, cardiovascular, abdomen, extremities, musculoskeletal, and neurological system.

A complete physical examination including weight will be performed at screening, Day -1 (baseline), and Weeks 2, 4, 6, 8, 12 (or early termination), and 14. Height will be measured at screening only. Height and weight will be measured with subjects not wearing shoes. Physical examination including weight will not be performed at COVID-19 related remote visits.

9.5.5. Electrocardiogram

A standard 12-lead ECG will be recorded in triplicate (at least 1 minute apart and within approximately 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. If needed, the investigator may consult with a local or central cardiologist to assist in the interpretation of an ECG. Based on the review of these parameters, the investigator or designee will note if the ECG is Normal, Abnormal not Clinically Significant, or Abnormal Clinically Significant. If the ECG is Abnormal Clinically Significant, the investigator or designee will provide a description of the abnormality recorded on the AE eCRF.

The 12-lead ECG will be conducted at screening, Day -1 (baseline), and Weeks 2, 4, 6, 8, 10, 12 (or early termination), and 14.

9.5.6. Clinical Laboratory Assessments

All clinical laboratory assessments will be performed by a central laboratory or at a local laboratory as needed. In addition, a urine pregnancy test will be performed by the study site on Day -1 (baseline) to confirm subject eligibility. The central laboratory will provide instructions and supplies before study initiation and instructions will be included in a laboratory manual. The laboratory test battery will include routine and screening laboratory tests. Fasting is not required for the clinical laboratory assessments. Select clinical laboratory assessments may be performed by a local lab (for re-testing or if the subject is not able to come to the study site); prior approval by the medical monitor is required.

The following clinical safety laboratory assays will be performed:

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

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

Prolactin: Serum prolactin samples will be shipped to a central laboratory for analysis. Prolactin results will remain blinded to investigators, subjects, and sponsor until database lock. The DSMB may review unblinded prolactin data during the course of the study.

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

The following additional laboratory tests will be performed:

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

Urine Drug Screen: The urine drug screen will test for amphetamines, barbiturates, benzodiazepines, cocaine, phencyclidine, and opiates. The urine drug screen will be collected at screening by the study site and analyzed by a central laboratory.

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 urine pregnancy tests will be performed at subsequent visits.

9.5.7. Columbia-Suicide Severity Rating Scale

The C-SSRS is a validated instrument to prospectively assess suicidal ideation and behavior (Posner et al., 2011). 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. Subjects with any lifetime suicidal behavior or suicidal ideation of type 4 (active suicidal ideation with some intent to act, without specific plan) or type 5 (active suicidal ideation with specific plan and intent) in the 3 months before screening based on the C-SSRS should be excluded (see exclusion criterion #10).

The C-SSRS will be administered and scored by the investigator or qualified study site personnel at screening, Day -1 (baseline), and Weeks 2, 4, 6, 8, 10, 12 (or early termination), and 14.

9.5.8. Barnes Akathisia Rating Scale

The Barnes Akathisia Rating Scale (BARS) is a validated four-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, subjects' awareness of restlessness and related distress), together with a global assessment of akathisia. Global assessment is made on a

scale of 0 to 5 (0=absent; 1=questionable; 2=mild akathisia; 3=moderate akathisia; 4=marked akathisia; 5=severe akathisia).

The BARS will be administered on Day -1 (baseline) and Weeks 2, 4, 6, 8, 10, and 12 (or early termination).

This assessment will not be conducted at COVID-19 related remote visits.

9.5.9. Hospital Anxiety and Depression Scale

The HADS is a commonly used instrument to determine the levels of anxiety and depression that a person is experiencing. The HADS is a 14-item scale; 7 of the items relate to anxiety and 7 relate to depression (Zigmond and Snaith, 1983). Each item is answered on a 4-point (0 to 3) response category so the possible scores range from 0 to 21 for anxiety and 0 to 21 for depression. The HADS has been validated as a measure of depression and anxiety (Barczak et al., 1988).

The HADS will be administered at screening, Day -1 (baseline), and Weeks 2, 4, 6, 8, 10, 12 (or early termination), and 14.

9.5.10. Unified Huntington's Disease Rating Scale

A subset of the UHDRS Motor Assessment (items rating retropulsion pull test, finger taps, pronate/supinate hands, rigidity-arms, and bradykinesia-body) will be used to assess for parkinsonism at each visit.

This assessment will not be conducted at COVID-19 related remote visits.

9.6. Other Assessment

9.6.1. Anosognosia Scale

The Anosognosia Scale (AS) is an instrument to screen for anosognosia in daily practice and is specific for HD (Deckel and Morrison, 1996). This scale requires subjects and investigators to rate the subject's ability to perform tasks relative to individuals of the subject's age and education on a five-point scale, rating 8 items.

The AS will be completed at the study site by both the subject and the investigator (or designee) at Day -1 (baseline) and Weeks 12 (or early termination) and 14. This assessment will not be performed at COVID-19 related remote visits.

9.7. Specific Study Period Information

After signing the ICF, subjects will undergo screening procedures within 4 weeks (28 days) of Day -1.

If individual in-person study visits at the study site are not possible due to COVID-19 related reasons (eg, subject is not able to travel to the site for safety reasons or as part of public health measures), remote visits may be conducted on a case-by-case basis at the judgment of the investigator and in consultation with the study medical monitor; once able, the subject is to return to in-person visits at the study site (see Appendix A). Screening, baseline, and study visits

at Weeks 10 and 12 must be performed at the study site; subjects who plan on entering Study NBI-98854-HD3006 the same day as Study NBI-98854-HD3005 Week 14 must have Week 14 follow-up performed at the study site.

9.7.1. Screening Period (Weeks -4 to -1)

Informed consent process: The ICF will be reviewed with subjects. The UBACC will then be administered (Jeste et al., 2007). Only subjects who are deemed to have the capacity to provide consent may sign the ICF. The ICF must be signed prior to the start of any screening procedures. Subject may also be asked to provide permission to share the video recordings of their UHDRS assessments for educational purposes, however this permission is not required for study participation. Subjects may refuse to sign the release form with no effect on their study eligibility.

[redacted]

During the first part of the screening visit, the UHDRS (motor, behavior, and TFC) will be administered and scored by the investigator (or qualified designee). The structured examination will be video recorded and uploaded to the central server.

After the ICF process and the UHDRS are complete, the following study procedures and assessments will be performed:

- Subjects will be read the treatment assignment script, which describes the placebo-controlled nature of the study.
- Assess inclusion/exclusion criteria.
- Collect medical history.
- Perform a physical examination (including height and weight).
- Collect vital signs.
- Perform 12-lead ECG in triplicate (at least 1 minute apart and within approximately 15 minutes).
- Perform a serum pregnancy test (β-hCG) only for female subjects of childbearing potential.
- Collect blood sample for serology testing (HIV-Ab, HBsAg, and HCV-Ab).
- Collect a blood sample for CAG repeat.
- Collect blood sample for hematology and clinical chemistry.
- Collect urine sample for urinalysis.
- Perform urine drug screen.
- Administer the HADS.

- Administer the C-SSRS (screening/baseline version).
- Administer the SDQ.
- Administer the CRS-PSP item #13 (only for subjects who score ≥11 on the SDQ and who may still be eligible for participation, per the judgement of the investigator).
- Record prior and concomitant medications.
- AE monitoring.
- [redacted]

9.7.2. Baseline (Day -1)

Subjects will return to the study site on Day -1. During the first part of the study visit, the full UHDRS will be administered and scored by the investigator or qualified designee. In addition, the motor portion of the UHDRS will be video recorded and uploaded to the central server.

After the UHDRS assessment, the following study procedures and assessments will be performed:

- Subjects will be read the treatment assignment script, which describes the placebo-controlled nature of the study.
- Update inclusion/exclusion criteria.
- Update medical history.
- Perform a physical examination (including weight).
- Collect vital signs.
- Perform 12-lead ECG in triplicate (at least 1 minute apart and within approximately 15 minutes).
- Perform a urine pregnancy test only for female subjects of childbearing potential.
- Collect blood sample for hematology and clinical chemistry.
- Collect blood sample for prolactin.

- Collect urine sample for urinalysis.
- Collect blood sample for genotyping.
- Collect blood sample for PK assessment.
- Administer the HADS.
- Administer the C-SSRS (Since Last Visit version).
- Administer the BARS.
- Administer the SF-36.
- Administer the Neuro-QoL Upper Extremity Function Short Form and the Lower Extremity Function Short Form.
- Administer the CGI-S.
- Administer the PGI-S.
- Administer the HD-HI.
- Administer the EQ-5D-5L.
- Administer the MoCA.
- Administer the AS.
- Randomization.
- Record concomitant medications.
- AE monitoring.
- [redacted]

The site will access the IWRS to obtain an identification number for a kit containing a 2-week supply of the study drug to be dispensed to eligible subjects.

At this visit, subjects will be instructed:

- To take study drug (in the presence of their caregiver, if applicable) each morning (starting on Day 1) at approximately the same time every day. The subjects may take the study drug with or without food and must swallow it with approximately 4 ounces of water or other liquid.
- To contact the study site immediately without waiting for the next study visit to report AEs or before starting any new medication.

- To return to the study site in approximately 2 weeks for their next study visit having taken their daily dose of study drug.
- To return all used and unused study drug and packaging at the next study visit.

9.7.3. Dose-Adjustment Period (Weeks 2 to 8 [±3 days])

All visits should be conducted at the study site. Due to COVID-19, in the event a subject is unable to attend an in-person visit, a select subset of assessments may be conducted at a remote visit (see Appendix A).

The following study evaluations and tasks will be performed at the study site:

- Perform a physical examination (including weight).
- Collect vital signs.
- Perform 12-lead ECG in triplicate (at least 1 minute apart and within approximately 15 minutes).
- Perform a urine pregnancy test only for female subjects of childbearing potential.
- Collect blood sample for hematology and clinical chemistry.
- Collect blood sample for prolactin (Week 8 only).
- Collect urine sample for urinalysis.
- Collect blood sample for PK assessment.
- Administer the HADS.
- Administer the C-SSRS (Since Last Visit version).
- Administer the BARS.
- Administer the UHDRS (motor and behavior portions only).
- Administer the Neuro-QoL Upper Extremity Function Short Form and the Lower Extremity Function Short Form (Weeks 4 and 8 only).
- Administer the PGI-C.
- Administer the CGI-C.
- Administer the CGI-S.
- Administer the PGI-S.
- Dispense study drug.
- Perform compliance check by counting the capsules returned.
- Record concomitant medications.
- AE monitoring.

9.7.4. Maintenance Period (Weeks 10 and 12 [or early termination; ±3 days])

All visits should be conducted at the study site. Due to COVID-19, in the event a subject is unable to attend an in-person visit, the early termination visit may performed remotely (see Appendix A).

The following study evaluations and tasks will be performed at the study site:

- Perform a physical examination (including weight) (Week 12 [or early termination] only).
- Collect vital signs.
- Perform 12-lead ECG in triplicate (at least 1 minute apart and within approximately 15 minutes).
- Perform a urine pregnancy test only for female subjects of childbearing potential.
- Collect blood sample for hematology and clinical chemistry.
- Collect blood sample for prolactin (Week 12 [or early termination] only).
- Collect urine sample for urinalysis.
- Collect blood sample for PK assessment.
- Administer the HADS.
- Administer the C-SSRS (Since Last Visit version).
- Administer the BARS.
- Administer the full UHDRS (motor and behavior portions only at Week 10, full UHDRS at Week 12), including video recording of the motor portion only.
- Administer the Neuro-QoL Upper Extremity Function Short Form and the Lower Extremity Function Short Form.
- Administer the PGI-C.
- Administer the CGI-C.
- Administer the CGI-S.
- Administer the PGI-S.
- Administer the SF-36 (Week 12 [or early termination] only).
- Administer the HD-HI.
- Administer the EQ-5D-5L.
- Administer the AS (Week 12 only).
- Dispense study drug (Week 10 only).
- Perform compliance check by counting the capsules returned.

- Record concomitant medications.
- AE monitoring.
- [redacted]

9.7.5. Follow-up Visit (Week 14 [±3 days] or 2 weeks following an early termination visit)

All visits should be conducted at the study site. Due to COVID-19, in the event a subject is unable to attend an in-person visit, the Week 14 follow up visit may be performed remotely (see Appendix A). Subjects who plan on entering Study NBI-98854-HD3006 the same day as Study NBI-98854-HD3005 Week 14 must have Week 14 follow up performed at the study site.

If a subject undergoes an early termination visit, the follow-up visit can be done in-person or remotely via telephone to assess subject safety off study drug.

The following study evaluations and tasks will be performed at the study site:

- Perform a physical examination (including weight).
- Collect vital signs.
- Perform 12-lead ECG in triplicate (at least 1 minute apart and within approximately 15 minutes).
- Perform a urine pregnancy test only for female subjects of childbearing potential.
- Collect blood sample for hematology and clinical chemistry.
- Collect blood sample for prolactin.

- Collect urine sample for urinalysis.
- Collect blood sample for PK assessment.
- Administer the HADS.
- Administer the C-SSRS (Since Last Visit version).
- Administer the full UHDRS.
- Administer the Neuro-QoL Upper Extremity Function Short Form and the Lower Extremity Function Short Form.
- Administer the PGI-C.
- Administer the CGI-C.
- Administer the CGI-S.
- Administer the PGI-S.
- Administer the AS.
- Record concomitant medications.
- AE monitoring.

9.7.6. Unscheduled Visit(s)

All visits should be conducted at the study site. Due to COVID-19, in the event a subject is unable to attend an in-person visit, unscheduled visits may be performed remotely (see Appendix A).

For unscheduled visit(s) needed during the course of the study that are due to AEs (including clinically significant laboratory abnormalities) or other safety or tolerability concerns (including dose decreases), the following study evaluations and tasks may be performed at the investigator's discretion:

- Perform a physical examination (including weight).
- Collect vital signs.
- Perform 12-lead ECG in triplicate (at least 1 minute apart and within approximately 15 minutes).
- Perform a urine pregnancy test only for female subjects of childbearing potential.
- Collect blood sample for hematology and clinical chemistry.
- Collect urine sample for urinalysis.
- Collect a blood sample for PK assessment (for unscheduled visits due to AEs within 48 hours of the most recent study drug dose).
- Administer the HADS.
- Administer the C-SSRS (Since Last Visit version).

- Administer the BARS.
- Administer the motor and behavior portion only of the UHDRS.
- Record concomitant medications.
- AE monitoring.

9.8. Study Duration

The expected duration of study participation for each subject is approximately 18 weeks, including up to 4 weeks (28 Days) of screening, a 12-week treatment period, and a follow-up visit 2 weeks after the final dose of study drug.

9.9. Prohibitions and Restrictions

9.9.1. Prior and Concomitant Medications

All prescription and over-the-counter (OTC) medications, including dietary and herbal supplements, taken by subjects during the 30 days before screening and during the study will be entered on the Prior and Concomitant Medications eCRF.

Medications that may prolong the QT interval: valbenazine may prolong the QT interval. Caution should be used when valbenazine is coadministered with medications known to prolong the QT interval.

Medications to treat medical conditions: All coexistent diseases or conditions will be treated in accordance with prevailing medical practice. Benzodiazepines and opiates must be at a stable dose (ie, no as-needed use) for 2 weeks before Day -1 (baseline). Antidepressant therapy must be at a stable dose (ie, no prn use) for 8 weeks before Day -1 (baseline). Investigators should document doses of current medication using medical or pharmacy records, confirmation with the subject's caregivers (if applicable), or through reliable subject-reported information (eg, provide a list of medications and doses).

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

- **Antipsychotics or other dopamine receptor blockers:** antipsychotics (eg, risperidone, olanzapine, quetiapine, aripiprazole, ziprasidone, chlorpromazine, haloperidol, fluphenazine, clozapine) and dopamine receptor blockers (eg, metoclopramide, domperidone) are prohibited.
- **CYP3A4 inducers:** Strong inducers of CYP3A4 (eg, phenytoin, phenobarbital, rifabutin, rifampin, primidone, St. John's Wort) are prohibited.
- **Dopamine agonists and precursors:** Dopamine receptor agonists (eg, ropinirole) and precursors (eg, carbidopa/levodopa) are prohibited.
- **MAOIs:** All MAOIs (eg, isocarboxazid, phenelzine, selegiline, tranylcypromine) are prohibited.

- **VMAT2 Inhibitors:** VMAT2 inhibitor medications ([redacted] valbenazine) are prohibited (except for valbenazine administered per the current protocol).

As needed (prn) use: As needed use of the following medications is prohibited, when administered systemically: anticholinergics, mood stabilizers, antidepressants, strong CYP3A4 inhibitors (eg, clarithromycin, diltiazem, grapefruit juice, itraconazole, ketoconazole, nefazodone), and strong CYP2D6 inhibitors (eg, bupropion, fluoxetine, paroxetine, quinidine). As needed use of benzodiazepines and opiates is allowed except within 48 hours before study visits. [redacted]

[redacted]

9.9.3. Other Restrictions

- Subjects must not donate blood within 30 days or donate plasma within 7 days of Day -1 (baseline) and until 30 days after the final study visit, early termination.
- Male subjects must agree to refrain from donating sperm for 90 days after the last dose of study drug.
- Subjects must continue using contraception for 30 days after the last dose of study drug for females and 90 days after the last dose of study drug for males.
- Participation in another investigational drug study is prohibited for at least 30 days after the last dose of study drug or 30 days after study completion, whichever is longer.

9.9.4. Caregiver Responsibilities

Caregivers of subjects are encouraged to be present at screening. After screening, subjects with a TFC score between 5 and 10 (inclusive) must have a reliable caregiver to ensure study drug administration and attendance at study visits. Subjects with a TFC of 5 to 7 should have a caregiver present or available by telephone at all study visits. For subjects with a TFC of 8 to 10, a caregiver should be present or available by telephone at the following visits: baseline and Weeks 6, 10 and 12. For visits at Weeks 2, 4, 8, and 14, caregivers of subjects with TFC 8 to 10 are encouraged to be present at these study visits; however, if attendance at these visits is not feasible, the caregiver must be available to be contacted by telephone at the time of the visit.

[redacted]

9.10. Discontinuation of Study Drug and Subject Withdrawal

Subjects can discontinue study drug or withdraw their consent to participate in the study at any time. The investigator must discontinue study drug dosing or withdraw any subject from the study if a subject requests study drug dosing to be discontinued or to be withdrawn from the study, respectively. All subjects prematurely discontinuing study drug dosing should continue study participation to be followed for safety and efficacy outcomes.

9.10.1. Discontinuation of Study Drug Dosing

If a subject prematurely discontinues study drug dosing, the investigator will record the reason for discontinuation on the relevant eCRF. Such subjects will not be automatically withdrawn from the study and should continue participation in the study. The investigator and subject should discuss a plan for continued participation. Data for any outcome measures, particularly the primary and secondary endpoints, as well as safety follow-up, are important to collect. For any subsequent study visits after study drug is prematurely discontinued, subjects will not be required to undergo PK sampling, [redacted]. If medically indicated, treatment with medication listed under Section 9.9.1 is no longer prohibited after study drug discontinuation. Subjects must wait a minimum of 2 weeks after discontinuation of study drug dosing before starting any symptomatic drug treatment for chorea.

The investigator must discontinue study drug dosing if the subject experiences any of the following:

- If the type, frequency, or severity of any AE becomes unacceptable/intolerable, despite attempts to decrease the dose.
- If the subject is unable to tolerate the lowest allowable study dose (20 mg).
- QTcF value >500 msec (cardiologist verified) on any ECG tracing.
- If the subject exhibits suicidal behavior, or suicidal ideation of type 4 (active suicidal ideation with some intent to act, without specific plan) or type 5 (active suicidal ideation with specific plan and intent) based on the C-SSRS.
- Subject is confirmed to be pregnant.

The investigator or NBI may discontinue study drug dosing for other reasons as described below.

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

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

9.10.2. Withdrawal from 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 early termination assessments performed. If a subject withdraws prematurely and an in-person visit cannot be conducted for any reason, including COVID-19, the subject will be asked to participate in the visit via telephone (see Appendix A). A safety follow-up call approximately 14 days after discontinuation of study drug should be performed.

Reasons for a subject's withdrawal from study are:

- The subject is lost to follow-up.
- Sponsor decision.
- Investigator decision.
- Subject death.
- Withdrawal of consent for the study.

9.10.3. Sponsor's Termination or Suspension of Study

The Sponsor or designee reserves the right to close a study site, terminate or suspend the entire study, or terminate or suspend the study at individual sites, at any time for any reason. If the study is prematurely terminated or suspended, 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 suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the subject and should assure appropriate therapy and/or follow-up.

10. STUDY DRUG

10.1. Study Drug Supplies

10.1.1. Valbenazine

NBI or its designee will provide the study site with a supply of study drug sufficient for the completion of the treatment period of the study.

Valbenazine will be supplied as orally administered capsules containing 20 or 40 mg of valbenazine (free base equivalents as the ditosylate salt). Subjects must swallow the capsules (2 capsules) with approximately 4 ounces of water or other liquid, with or without food. The dosing regimens and valbenazine capsules that will be used in this study are shown in Table 3.

Table 3: Dosing Regimens and Number of Valbenazine Capsules

Dose	Valbenazine 20 mg capsule	Valbenazine 40 mg capsule	Placebo capsule
Valbenazine 20 mg	1	--	1
Valbenazine 40 mg	2	--	--
Valbenazine 60 mg	1	1	--
Valbenazine 80 mg	--	2	--
Placebo	--	--	2

10.1.2. Placebo

Matching placebo capsules are identical in appearance to valbenazine and will be orally administered in a double-blind manner (2 placebo capsules) on an identical schedule as valbenazine. Subjects must swallow the capsules with approximately 4 ounces of water or other liquid, with or without food.

10.2. Study Drug Storage

All capsules must be stored at controlled room temperature ([redacted]).

Study drug must be stored and inventoried according to applicable state and federal regulations and study procedures.

10.3. Study Drug Packaging and Labeling

All packaging and labeling operations will be performed according to Good Manufacturing Practice (GMP) and GCP. The study drugs will be sent to designated staff at the study site who must complete and return a drug supply confirmation to NBI or its designee verifying the receipt of the drug. Study drug will be labeled in accordance with federal and local regulations, as applicable.

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

10.4. Blinding

This study includes a 12-week double-blind placebo-controlled treatment period during which the subject, investigator, all study site personnel, and the sponsor (or designee) will be blinded to the subject's treatment. During this treatment period, all subjects will receive valbenazine or placebo as two capsules (identical in appearance) to be self-administered once daily. Clinical trial material supply chain personnel who are not involved in decisions regarding subject's study treatment will not be blinded.

The randomization code will be broken for an individual subject only if the subject is pregnant, experiences an SAE that the investigator feels cannot be adequately treated without knowing the

identity of the subject's treatment assignment, or for regulatory reporting requirements. After the randomization code is broken because of a pregnancy, the subject will be informed of her treatment assignment. In the case of a medical emergency in which knowledge of the identity of the study treatment is important for subject management, the investigator has the responsibility to decide whether to break the blind; treatment assignments would be unblinded using IWRS. It is recommended that the investigator contact the Study Medical Monitor (or designee; refer to Section 11.4.3 for contact information) before unblinding if it would not result in unnecessary delay to the immediate medical management of the subject. Documentation of the unblinding must be maintained.

Members of the DSMB and individuals who generate the DSMB reports will be unblinded throughout the study.

10.5. Study Drug Preparation and Administration

Study drug will be self-administered (in the presence of the subject's caregiver, if applicable) once daily (qd) starting on Day 1. Study drug should be administered at approximately the same time each day during the study. If a subject forgets or is unable to take the study drug during this time period, the subject should take his or her daily dose of study drug as soon as possible but no later than 2400 hours. The subject will need to skip the dose for that day if he or she is unable to take the study drug before 2400 hours. Subjects or their caregivers will record the date and time of study drug dosing each day on the form provided as part of the study drug packaging.

10.6. Study Drug Compliance and Accountability

Subjects will bring all unused study drug and empty drug packaging material to the site at specified study visits for drug accountability and reconciliation by study site personnel. A compliance check will be performed by counting the capsules returned at each study visit. In the case where a subject is unable to return used and unused study drug to the study site, the subject may ship them directly to the study site at the instruction of the investigator.

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

10.7. Study Drug Return

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

Returns will be shipped to the Sponsor or its designee according to instructions provided by the Sponsor or its designee and according to applicable local and national regulations and study procedures unless alternate disposition of the study treatment is approved by the Sponsor.

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

11. ADVERSE EVENTS

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

11.1. Definition

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

AEs include, but are not limited to: (1) a worsening or change in nature, severity, or frequency of conditions present at the start of the study; (2) intercurrent illness; and (3) drug interaction. Subject deterioration due to HD beyond what would otherwise be expected due to the natural history of the disease should be reported as an AE.

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

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

The following are not considered AEs:

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

11.1.1. Intensity of Adverse Events

AEs must be graded for intensity. An intensity category of mild, moderate, or severe, as defined in Table 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 adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	An adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
Severe	An adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

11.1.2. Relationship to Study Drug

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

Table 5: Relationship of Adverse Events to Study Drug

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

11.2. Recording Adverse Events

Each AE will be documented on the AE eCRF. The investigator (or designee) will provide information on dates of onset and resolution, intensity, seriousness, frequency, action(s) taken, changes in study drug usage, relationship to study drug, and outcome.

The following categories of medical events that could occur during participation in a clinical study must be reported within 24 hours to the study medical monitor and NBI Drug Safety and Pharmacovigilance (DSPV):

- SAE, including death.
- Pregnancy.
- Treatment unblinding for any reason.
- Events of suicidal behavior or suicidal ideation type 4 (active suicidal ideation with some intent to act, without specific plan) or type 5 (active suicidal ideation with specific plan and intent) based on the C-SSRS.

11.3. Poststudy Follow-Up of Adverse Events

All AEs, including clinically significant changes in ECGs, physical examination findings, or isolated clinically significant laboratory findings must be followed until the event resolves, the condition stabilizes, the event is otherwise explained, or the subject is lost to follow-up.

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

11.4. Serious Adverse Events

All SAEs will be recorded from the time the subject has signed the ICF until 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 becomes aware 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 11.4.3.

11.4.1. Definition of a Serious Adverse Event

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

- Death.
- A life-threatening AE. Life-threatening means that the subject was, in the view of the investigator or Sponsor, at immediate risk of death from the reaction as it occurred. It does not mean that hypothetically the event might have caused death if it occurred in a more serious form.
- Inpatient hospitalization or prolongation of existing hospitalization. Hospitalization for elective treatment or a pre-existing condition that did not worsen during the clinical investigation is not considered an AE. Hospitalization or nursing home admission for the purpose of caregiver respite is not considered an AE. Complications that occur during

hospitalization are AEs, and if a complication prolongs hospitalization, the event is considered serious. Treatment in a hospital emergency room is not a hospitalization.

- A persistent or significant incapacity or substantial disruption of a person's ability to conduct normal life functions.
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization. These events may be considered serious when, based on appropriate medical judgment, they may jeopardize the health of the subject and may require medical or surgical intervention to prevent one of the outcomes listed. Any other event thought by the investigator to be serious should also be reported, following the reporting requirements detailed in this section. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

11.4.2. Managing Serious Adverse Events

Subjects experiencing an SAE or an emergency situation will be examined by a physician as soon as possible. The physician in attendance will do whatever is medically needed for the safety and well-being of the subject. The subject will remain under observation as long as medically indicated. Appropriate laboratory studies will be conducted until all parameters return to normal or are otherwise explained or stable. The subject will be followed until the SAE resolves or until the subject is medically stabilized. The investigator (or designee) will notify the Study Medical Monitor and NBI DSPV Department (and the IRB/IEC, if necessary) immediately (within 24 hours) of the SAE and the outcome of the SAE as described in Section 11.4.3.

11.4.3. Reporting Serious Adverse Events and Other Immediately Reportable Events

SAEs and other immediately reportable events (defined in Section 11.2) must be reported within 24 hours of first knowledge of the event by study personnel to the Study Medical Monitor and NBI DSPV Department. Reports of SAEs and pregnancies must be followed by a fax or email of the SAE or Pregnancy Form. It is important that the investigator provides his or her assessment of relationship to study drug at the time of the initial SAE report.

For SAEs and other immediately reportable events, contact DSPV and Study Medical Monitor:

DSPV telephone: [redacted]
DSPV facsimile: [redacted]
DSPV e-mail: [redacted]
Study Medical Monitor: **Telephone:** [redacted]
Cell phone: [redacted]

11.4.4. Expedited Safety Reports

NBI or its representatives will submit an Expedited Safety Report for any suspected adverse reaction (as defined in Section 11.1.2) that is considered both serious and unexpected within

15 calendar days and for any unexpected fatal or life-threatening experience within 7 calendar days to the applicable regulatory authority(ies); or according to country-specific regulations.

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

11.5. Pregnancy

Pregnancy is neither an AE nor an SAE unless the criteria for an SAE are met. However, all pregnancies in female subjects who received valbenazine will be followed to assess for congenital anomaly. Subjects must be counseled at all visits to continue using contraception (see inclusion criterion #7) until 30 days (females) or 90 days (males) after the last dose of study drug. If at any time between the time the subject signs the ICF and the last study visit, a subject believes she is pregnant, the subject will be instructed to return to the study site within 24 hours and undergo a serum pregnancy test to confirm pregnancy.

All confirmed pregnancies in subjects who received study drug must be immediately reported to NBI (see Section 11.4.3 for contact information), followed by fax or email of the pregnancy form to NBI DSPV. A first trimester ultrasound will be requested for all confirmed pregnancies. Pregnancies in subjects who received valbenazine will be followed until resolution (ie, termination [voluntary or spontaneous] or birth).

12. DOCUMENTATION OF DATA

12.1. Case Report Forms

The eCRF data for this study are being collected with an EDC system [redacted]. The EDC system and the study-specific eCRFs will comply with Title 21 CFR Part 11. The documentation related to the validation of the EDC system is available through the vendor, [redacted], while the validation of the study specific eCRFs will be conducted by [redacted] in conjunction with NBI, and the required documentation will be maintained in the Trial Master File.

The site investigator will document subject data in his/her own subject files and worksheets provided by [redacted]. These subject files and worksheets 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 specific data captured in an electronic format, which will be sent electronically from the vendor and may be uploaded into the database [redacted]. All data entered into the eCRF will be supported by source documentation. The eCRF for each subject must be reviewed by the investigator and signed on the appropriate eCRF page(s). This should be done as soon as possible after the subject completes the study visit.

The site investigator or an authorized member of the site 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 and acceptability by NBI (or designee). NBI (or designee) will also be allowed access to all source documents and medical records pertinent to the study in order to verify eCRF entries. The site investigator will review the eCRFs for completeness and accuracy and enter his or her electronic signature on the eCRF page(s) as applicable as evidence thereof after each study visit.

The CRO will provide NBI (or designee) and the study sites with access to the study EDC system [redacted] for the duration of the study through a password-protected method of internet access. Such access will be removed from study sites at the end of the site's participation in the study. Data from the EDC system will be archived on appropriate data media and provided to the site investigator at that time as a durable record of the site's eCRF data. Although not required, the site investigator may make paper printouts from that media. All subject eCRF data will also be provided to NBI via an agreed transfer method and in an agreed format.

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

12.2. Data Capture, Review, and Validation

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

12.3. Coding Dictionaries

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

13. STATISTICAL AND ANALYTICAL PLAN

13.1. Overview

Descriptive and inferential statistical methods will be used to evaluate and summarize the data from this study. The term "descriptive statistics" refers to the number of subjects (n), mean, median, SD, SEM, minimum, and maximum for continuous and ordinal categorical variables; and refers to the number and percentage of subjects for categorical variables. Additional descriptive statistics may be presented for selected variables. The term "inferential statistics" refers to hypothesis tests which will be performed to assess differences between the valbenazine treatment group and the placebo treatment group for selected efficacy variables.

The analysis plan provided in this protocol represents a brief description of the planned analyses. The comprehensive statistical analysis plan (SAP) will be generated prior to final study database lock.

13.2. Analysis Sets

Two primary analysis sets will be defined for this study. The safety analysis set will include all subjects who are randomized to a treatment group, take at least one dose of study drug, and have any postbaseline safety data. The full analysis set (FAS) will include all subjects who are randomized to a treatment group and who have at least one evaluable TMC change from baseline score during the 12-week double-blind treatment period. Additional analysis sets may be specified in the SAP.

13.3. Sample Size Determination

A total sample size of 120 subjects (60 per group) will provide >95% power to detect a difference between the valbenazine and placebo treatment groups in the change from the screening period baseline (the average of the screening and Day -1 assessments) to maintenance (the average of the Week 10 and Week 12 assessments) in the TMC based on on-site assessments, using a two-sample t-test with a two-sided Type I error of 0.05. This assumes a difference in means of 2.4 with a common SD of 3.3. The specified treatment effect is attenuated to account for up to 4 (6.7%) subjects per treatment group who prematurely discontinue study drug dosing.

The above sample size and power estimates were obtained from [redacted].

13.4. Handling of Missing Data

Methods for handling missing data for the primary and secondary efficacy endpoints are discussed in Section 13.10. Any additional methods or details for the handling of missing data will be described in the SAP.

13.5. Disposition of Subjects

The summary of subject enrollment and disposition will display the number of subjects who were randomized to each treatment group, who completed the dose-adjustment period (ie, up to Week 8), who competed the dose maintenance period (ie, up to Week 12), and who completed

the study. The number of subjects who discontinued study drug dosing early or did not complete the study will also be summarized, both overall and by reason. Additional summaries may also be included.

A separate summary of randomization by study site will be presented. This summary will display the number of subjects randomized to each treatment group by site.

13.6. Important Protocol Deviations

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

13.7. Demographics and Baseline Subject Characteristics

Demographic data (age, sex, race, and ethnicity) and baseline characteristics (including, but not limited to: height, weight, BMI, [redacted] genotype status, and baseline values for the TMC score) will be summarized with descriptive statistics. Medical history will be summarized according to MedDRA System Organ Class (SOC) and Preferred Term (PT).

13.8. Study Drug Dosing and Compliance

The number and percentage of subjects who are dose compliant (at least 80% of expected number of doses taken) will be summarized with descriptive statistics by visit (Weeks 2, 4, 6, 8, 10, and 12).

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

13.9. Pharmacokinetics

The plasma concentrations of valbenazine and the metabolite NBI-98782 will be summarized with descriptive statistics by visit (Day -1 and Weeks 2, 4, 6, 8, 10, 12, and 14) and dose (last dose received prior to blood sample being drawn). Concentrations below the lower limit of quantification will be set equal to zero for all plasma concentration summaries.

13.10. Efficacy Data

The efficacy measures in this study include the UHDRS, PGI-C, CGI-C, PGI-S, CGI-S, SF-36, Neuro-QoL, EQ-5D-5L, HD-HI, [redacted]. Several derived variables based on these measures (eg, the SF-36 Physical Component Summary) will be summarized with descriptive statistics. Selected variables will include inferential statistics. Unless otherwise specified, the FAS will be used as the primary analysis set for all efficacy measures. Regardless of adherence to study drug at the time of the assessment, all collected data will generally be included in the analyses. The SAP will provide a full description of the derived variables and analyses that will be summarized for these efficacy measures.

13.10.1. Primary Efficacy Endpoint

The primary efficacy endpoint for this study is the change from the screening period baseline (the average of the screening and Day -1 assessments) to maintenance (the average of the

Week 10 and Week 12 assessments) in the TMC based on on-site assessments. Changes from the screening period baseline to each postbaseline study visit (Weeks 2 through 12) are exploratory efficacy endpoints.

Descriptive statistics will be presented by treatment group for the TMC observed values, and changes from the screening period baseline at each visit and at maintenance. The changes from baseline to each postbaseline visit during the treatment period will be analyzed using a mixed-effect model repeated measures (MMRM) analysis. The model will include the screening period baseline TMC as a covariate, and treatment group, visit, treatment group-by-visit interaction, and baseline-by-visit interaction as fixed effects. Subject will be included as a random effect. Treatment group comparisons of the valbenazine treatment group vs. placebo at maintenance and each visit will be performed by constructing linear contrasts (or equivalent programming code) for differences between treatment group least-squares (LS) means. The LS means and differences in LS means will be presented in summary tables, along with the associated 95% confidence intervals. The treatment difference for the primary endpoint (maintenance) will be considered statistically significant if the two-sided p value is <0.05. Nominal (raw) two-sided p values for testing the significance of the treatment differences at the individual postbaseline visits will also be reported in the summary tables.

Any additional supportive or sensitivity analyses of the TMC change from screening period baseline to maintenance will be described in the SAP.

13.10.2. Secondary Efficacy Endpoints

CGI-C Responder Endpoint

CGI-C response status at Week 12 will be a secondary efficacy endpoint. Subjects whose CGI-C score is either a 1 ("very much improved") or a 2 ("much improved") will be classified as responders. Response statuses at Weeks 2 through 10 are exploratory efficacy endpoints.

Descriptive statistics will be presented by treatment group for the number and percentage of subjects classified as responders at each postbaseline visit. Analyses comparing the valbenazine treatment group to placebo will be performed using the Fisher exact test. Missing data at Week 12 will be imputed using non-responder imputation. Nominal two-sided p values for testing the significance of treatment group will be reported in summary tables; however, interpretation of the p value for the treatment group comparison at Week 12 will be based on a procedure which controls for multiple comparisons (Section 13.10.3).

PGI-C Responder Endpoint

PGI-C response status at Week 12 will be a secondary efficacy endpoint. The definition of response and analyses will be identical to those described for the CGI-C responder endpoint.

Neuro-QoL Upper Extremity Function

The change from baseline (Day -1) to Week 12 in the Neuro-QoL Upper Extremity Function T-score will also be a secondary endpoint. Change from baseline to Weeks 4, 8, and 10 are exploratory efficacy endpoints.

Descriptive statistics will be presented by treatment group for the observed values and changes from baseline at each visit. The changes from baseline to each postbaseline visit during the

treatment period will be analyzed using MMRM. The MMRM model will be similar to the model described above for the TMC analysis, with the exception that the covariate in the model will be the baseline value (Day -1) of the Neuro-QoL Upper Extremity Function T-score, and only visits where Neuro-QoL is scheduled to be collected will be included. Nominal two-sided p values for testing the significance of treatment group differences and associated 95% confidence intervals will be reported in summary tables; however, interpretation of the p value for the treatment group comparison at Week 12 will be based on a procedure which controls for multiple comparisons (Section 13.10.3).

Neuro-QoL Lower Extremity Function

The change from baseline (Day -1) to Week 12 in the Neuro-QoL Lower Extremity Function T-score will also be a secondary endpoint. The analyses will be identical to those described for the Neuro-QoL Upper Extremity Function.

13.10.3. Procedure to Control for Multiple Comparisons

A fixed-sequence testing procedure will be used to control the family-wise error rate for the primary and secondary efficacy endpoints. Testing of hypotheses at each step of the procedure commences only if all null hypotheses of the prior steps were rejected. The fixed-sequence testing procedure will consist of performing the hypothesis tests in the following prespecified order:

1. Primary endpoint: TMC change from screening period baseline to maintenance (valbenazine versus placebo treatment group).
2. Secondary endpoint: CGI-C response at Week 12 (valbenazine versus placebo treatment group).
3. Secondary endpoint: PGI-C response at Week 12 (valbenazine versus placebo treatment group).
4. Secondary endpoint: Neuro-QoL Upper Extremity Function change from baseline to Week 12 (valbenazine versus placebo treatment group).
5. Secondary endpoint: Neuro-QoL Lower Extremity Function change from baseline to Week 12 (valbenazine versus placebo treatment group).

Each step in the sequential testing procedure uses a local two-sided 0.05 level of significance for the null hypothesis being tested. The null hypothesis at each step of the procedure can only be rejected if all null hypotheses in prior steps were rejected.

13.10.4. Exploratory Endpoints

Endpoints not described in the preceding paragraphs are considered exploratory endpoints. Details regarding the definitions and analyses of these endpoints will be provided in the SAP.

13.11. Safety Data

Treatment-emergent adverse events (TEAEs), categorized by MedDRA SOC and/or PT will be summarized in frequency tables. The TEAE summary tables will include the number and

percentage of unique subjects experiencing each event. Summary tables will be presented for all TEAEs, severe TEAEs, TEAEs leading to study drug dose reduction, TEAEs leading to early discontinuation of study drug dosing, and SAEs.

An AE overview summary table will be provided which summarizes the number and percentage of subjects with any TEAE, any TEAE leading to study drug dose reduction, any TEAE leading to discontinuation of study drug dosing, any SAE, and any TEAE resulting in death. The summary table will also include the maximum TEAE intensity (mild, moderate, severe) reported for each subject.

Clinical laboratory, vital signs, ECG, C-SSRS, UHDRS motor score (items for parkinsonism), BARS, and HADS data will be summarized with descriptive statistics. Potentially clinically significant (PCS) values for selected clinical laboratory and vital signs variables will be summarized. Prior and concomitant medications will be summarized according to WHO Drug Anatomical Therapeutic Chemical Classification (ATC) categories.

13.12. Software

Statistical calculations and summaries will be generated using [redacted].

13.13. Interim Analysis

An interim analysis is not planned for this study.

14. REGULATORY AND ETHICAL ISSUES

14.1. General Legal References

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

14.2. Institutional Review Board/Independent Ethics Committee

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

14.3. Protocol Adherence – Amendments

The protocol must be read thoroughly, and the instructions must be followed exactly. Any changes in the protocol will require a formal amendment. Such amendments will be agreed upon and approved in writing by the investigator and NBI. The IRB/IEC will be notified of all

amendments to the protocol. Amendments to the protocol will not be implemented until written IRB/IEC approval has been received.

Any changes in protocol conduct necessary to immediately assure subject safety may be immediately implemented without subsequent review by the IRB and notification to the FDA. These changes must be documented as protocol deviations (until protocol amendment is approved).

14.4. Required Documents

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

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

14.5. Informed Consent

All subjects will provide informed consent before the performance of any study-related procedures. Initial consent at screening must be performed at the study site. Due to COVID-19, instances of reconsent may be performed remotely (process described in Appendix A).

Each subject's chart will include the signed ICF for study participation. When the study treatment is completed and the eCRF has been monitored, the ICF will be kept in the investigator's central study file. Regulatory authorities may check the existence of the signed ICF in this central study folder if not having done so during the study.

14.6. Study Monitoring

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

Upon completion of the study, the study monitor will arrange for a final review of the study files after which the files should be secured for the appropriate time period. The investigator or appointed delegate will receive the study monitor during on-site visits, provide appropriate

documentation electronically for remote visits, will cooperate in providing the documents for inspection, and will respond to inquiries. In addition, the investigator will permit inspection of the study files by authorized representatives of the regulatory agencies.

14.7. Quality Assurance

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

14.8. Record Retention

Study records should be retained in compliance with the federal regulations and those of the study site.

NBI 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, NBI must be informed of the individual who will be assuming this responsibility.

14.9. Confidentiality

NBI or its designee, and the study site affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, all data will be identified only by an identification number.

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

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

15. STUDY COMMENCEMENT AND DISCONTINUATION

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

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

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APPENDIX A. GUIDANCE TO ADDRESS GLOBAL HEALTH EMERGENCIES AND POTENTIAL IMPACT ON THE CLINICAL STUDY

Due to the global COVID-19 pandemic and in alignment with guidance put forth by the US Food and Drug Administration (FDA; Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency [March 2020, updated December 2020]) and Health Canada (Management of Clinical Trials During the COVID-19 Pandemic: Notice to Clinical Trial Sponsors [September 2020]), the following revisions have been made in the event that a subject is unable to attend an in-person visit (eg, subject is unable to travel to the site for safety reasons or as part of public health measures). Remote visits are to be conducted on a case-by-case basis at the judgement of the investigator and in consultation with the study medical monitor; once able, the subject is to return to in-person visits at the study site.

Informed Consent

In the situation where reconsent is necessary (eg, updated ICF, protocol amendments, etc.) and the subject is unable to print the informed consent document provided electronically by the investigator and an electronic signature process is not available, the investigator may consider using the following alternative process for obtaining and documenting informed consent. This process is not applicable for initial ICF signing at the screening visit which must be performed at the study site.

1. The investigator provides the subject with an electronic version of the informed consent document.
2. The investigator arranges a telephone call with the subject, the investigator, a witness who is not otherwise connected with the study and, if desired and feasible, additional participants requested by the subject. Alternatively, in lieu of having a witness present, the conversation may be recorded.
3. To ensure that all subjects are treated consistently, a standard process should be used that will accomplish the following:
    - Identification of who is on the call.
    - Review of the informed consent document with the investigator and responses to any questions the subject may have.
    - Verbal confirmation by the subject that their questions have been answered and that they agree to participate in the study.
4. Verbal confirmation by the subject that they signed and dated a blank piece of paper with a written statement that they voluntarily agree to participate in the study, noting both the protocol number and brief protocol title.
5. After signing and dating the newly created document, the subject sends a photograph of the signed and dated statement by facsimile, text message, or email to the investigator. The subject may also return the document to the investigator by mail at a later date, or at a future study visit that may occur at the study site.

6. When using a witness, documentation in the study records includes a signed and dated attestation by the witness who participated on the call that the subject confirmed their agreement to participate in the study and signed the document referenced above.
7. When using a recording in lieu of using a witness, documentation in the study records includes the recording of the conference call.
8. After the signed and dated document is received by study staff, it should be appended to a copy of the consent document that was reviewed with the subject and retained in the study records as would normally be done for a signed informed consent document. Additionally, a note should be made in the study records explaining the reason why informed consent was obtained through an alternative method. The case history for each subject must document that informed consent was obtained prior to participation in the study.

Data Collection, Transfer, and Storage

When an assessment is conducted remotely, the investigator will document the date of the assessment, the person who conducted the assessment, and the type of technology used. Remote data acquisition, transmission, and storage will be secured, and the privacy of study subjects will be protected. Any electronic platforms used to transmit data into study records will include automated audit trails.

Communication during remote visits between the investigator, subject, and home health professional will be conducted by audio telephone call.

Remote Study Visits and Assessments

Study Visits 3 to 6 (Weeks 2 to 8) and Study Visit 9 (Week 14) have a window of ±3 days. The following sequence of events must be completed within this visit window (see Table 6 for full list of assessments):

1. Remote visit and dosing decision (approximately 1 day).
    a. Vitals, ECG, and urine and blood samples are collected.
    b. Patient-reported outcome (PRO) assessments (HADS, PGI-C, PGI-S, and Neuro-QoL) are completed.
    c. Investigator and/or qualified designee conducts telephone call with subject and home health professional to conduct the investigator assessments per Table 6.
    d. Home health professional reports vitals and ECG values to investigator via telephone call.
    e. Investigator reviews initial data obtained over telephone call and makes dosing decision based on tolerability.
2. Shipment of study drug kit directly to subject (at least 1 full day).
3. Subject receives study drug kit. Investigator confirms dosing decision after full assessment of data obtained at remote visit.
4. Subject begins dosing from the new study drug kit, as instructed by the investigator.

It is the responsibility of the investigator, not the home health professional, to assess the data obtained during the remote visit.

The investigator should make all attempts to prevent any gaps in dosing.

Table 6 presents the visits and assessments that may be conducted remotely. Assessments will be conducted by a home health professional, the subject, and the investigator and/or qualified designee as indicated below.

Table 6: Schedule of Remote Assessments for Subjects Impacted by COVID-19

Procedure[a]	Performed by	Dose-Adjustment Period					Follow-up	ET	Unscheduled[b]
	Week[c]	Day 1	2	4	6	8	14[d]	NA	NA
	Visit[c]	--	3	4	5	6	9	NA	NA
Vital signs	Home health professional[e]		X	X	X	X	X	X	X
12-lead ECG[f]	Home health professional[e]		X	X	X	X	X	X	X
Pregnancy test[g]	Home health professional[e]		X (u)	X (u)	X (u)	X (u)	X (u)	X (u)	X
Clinical laboratory tests[h]	Home health professional[e]		X	X	X	X	X	X	X
Blood sample for prolactin	Home health professional[e]					X	X	X	
Blood for PK assessments[i]	Home health professional[e]		X	X	X	X	X	X	X
Study drug accountability[j]	Home health professional[e]		X	X	X	X			
HADS	Subject[k]		X	X	X	X	X	X	X
PGI-C	Subject[k]		X	X	X	X	X	X	
PGI-S	Subject[k]		X	X	X	X	X	X	
Neuro-QoL[l]	Subject[k]			X		X	X	X	
C-SSRS	Investigator[m]		X	X	X	X	X	X	X
UHDRS (full, excluding motor and cognition)	Investigator[m]						X	X	
UHDRS (behavior)	Investigator[m]		X	X	X	X			X
AE monitoring	Investigator[m]		X	X	X	X	X	X	X
Prior and concomitant medications	Investigator[m]		X	X	X	X	X	X	X
Ship study drug	Study site[n]		X	X	X	X			
Study drug dosing[o]	Subject[j]	X	X	X	X	X			

AE=adverse event; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ET=early termination; HADS=Hospital Anxiety and Depression Scale; NA=not applicable; Neuro-QoL=Quality of Life in Neurological Disorders; PGI-C=Patient Global Impression of Change; PGI-S=Patient Global Impression of Severity; PK=pharmacokinetic; QTcF=corrected QT interval using Fridericia's formula; s=serum; TFC=Total Functional Capacity; u=urine; UHDRS=Unified Huntington's Disease Rating Scale.

[a] As much as possible, all remote study visits should occur at approximately the same time of day to standardize the time of day for the assessment of efficacy, safety, and drug exposure.

[b] Assessments during unscheduled visits may be performed at the investigator's discretion.

[c] Day 1 is the first day of dosing; study drug will be self-administered. Study visits 3 to 6 and study visit 9 (end of Weeks 2, 4, 6, 8 and 14) have a visit window of ±3 days.

[d] Final study visit (±3 days) for subjects who complete the study; subjects who withdraw from the study should complete an early termination visit (ie, assessments listed for the Week 12 visit). Subjects may discontinue study drug dosing, but should continue participation in the study.

[e] Home health professional will be responsible for obtaining vital signs, ECG, pregnancy test, clinical laboratory tests, blood samples for prolactin and PK assessments, and recording study drug accountability.

[f] A standard 12-lead ECG will be conducted in triplicate (at least 1 minute apart and within approximately 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).

[g] Pregnancy tests are required for women of childbearing potential.

[h] Clinical laboratory tests include hematology, clinical chemistry, and urinalysis. All blood samples will be obtained under non-fasted conditions.

[i] Subjects will be asked to record and provide dosing times on the days during the treatment period when blood PK samples are collected.
[j] Subjects will return all used and unused study drug and a compliance check will be performed by counting the capsules returned at each study visit.
[k] Subject will be provided HADS, PGI-C, PGI-S, and Neuro-QoL questionnaires to be self-administered.
[l] The Neuro-QoL assessments will include both the Upper Extremity Function Short Form and the Lower Extremity Function Short Form.
[m] UHDRS, C-SSRS, AEs, and prior and concomitant medications will be assessed by the investigator or qualified designee via a telephone call with subject.
[n] Study site will ship study drug kit directly to subject.
[o] Subject will take study drug at home at approximately the same time of day each day.