CLINICAL STUDY PROTOCOL

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A PHASE 3, OPEN-LABEL, SAFETY AND TOLERABILITY STUDY OF NBI-98854 FOR THE TREATMENT OF TARDIVE DYSKINESIA

Study No.: NBI-98854-1402

Development Phase: Phase 3

Sponsor: Neurocrine Biosciences, Inc.
12780 El Camino Real
San Diego, CA 92130
Telephone: (858) 617-7600
Facsimile: (858) 617-7705

CONFIDENTIAL

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

- Established principles of Good Clinical Practice (GCP) (Harmonized)
- United States (US) Code of Federal Regulations (CFR); US Food and Drug Administration (FDA)

CLINICAL STUDY TITLE:
A Phase 3, Open-Label, Safety and Tolerability Study of NBI-98854 for the Treatment of Tardive Dyskinesia

PROTOCOL NO: **NBI-98854-1402**

SITE:

_____
(Site Name)

PRINCIPAL INVESTIGATOR:

_____
(Principal Investigator Name)

As Agreed:

_____ _____
Date Principal Investigator

Accepted for the Sponsor:

SPONSOR:

Neurocrine Biosciences, Inc.
12780 El Camino Real
San Diego, CA 92130
Telephone: (858) 617-7600
Facsimile: (858) 617-7705

07 Dec 2015
Date

[redacted]
Chief Medical Officer

LIST OF PERSONNEL:

Sponsor:
Neurocrine Biosciences, Inc.
12780 El Camino Real
San Diego, CA 92130

Director, Clinical Programs:
Telephone:
Facsimile:
Cell Phone:

Medical Monitor:
Telephone:
Facsimile:
Cell Phone:

Serious Adverse Event Reporting:
Telephone:
Facsimile:
E-mail:

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1. STUDY SYNOPSIS

Title:	A Phase 3, Open-Label, Safety and Tolerability Study of NBI-98854 for the Treatment of Tardive Dyskinesia
Protocol Number:	NBI-98854-1402
Development Phase:	Phase 3
Study Sites:	Approximately 50 study sites in North America and Puerto Rico.
Study Objectives:	To evaluate the safety and tolerability of NBI-98854 (titrated from 40 to 80 mg) administered once daily for up to 12 months for the treatment of Tardive Dyskinesia (TD).
Overview of Study Design:	This is a Phase 3, open-label, fixed-dose titration study to evaluate the safety and tolerability of NBI-98854 (titrated from 40 mg to 80 mg) administered once daily (qd) for a total of 48 weeks of treatment. This study will enroll approximately 180 medically stable male and female subjects with clinical diagnoses of schizophrenia or schizoaffective disorder with neuroleptic-induced TD or mood disorder with neuroleptic-induced TD. All subjects must sign an informed consent form (ICF) prior to the conduct of any study related procedures, including washout of medications disallowed in the study. 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. Subjects will also be asked to sign an optional release form to allow their Abnormal Involuntary Movement Scale (AIMS) video recordings to be used for educational purposes. Subjects will be screened for eligibility for up to 6 weeks prior to Day -1 (baseline visit). On Day -1, eligible subjects will receive a supply of NBI-98854 40 mg qd for the first 4 weeks of the treatment period. Beginning on Day 1, study drug will be self-administered at home (in the presence of their caregiver, if applicable) in the morning between 0700-1000 hours. At the end of Week 4, the investigator may escalate the subject's dose to 80 mg or continue with the subject's current dose. A dose escalation will be allowed at the end of Week 4 if (1) the investigator or designee's assessment of the Clinical Global Impression – Tardive Dyskinesia (CGI-TD) is "minimally improved", "not changed", "minimally worse", "much worse", or "very much worse", and (2) the safety and tolerability of the current dose is acceptable as determined by a physician. The subject will then continue at the 80 mg dose until the end of the treatment period (end of Week 48). At any time after a dose escalation, the investigator may decrease the dose to 40 mg if the subject is unable to tolerate the dose increase. The subject will then continue at the 40 mg dose until the end of the treatment period (end of Week 48). Subjects who are unable to tolerate the starting dose of 40 mg or the resumption of 40 mg will be discontinued from the study. Subjects will return to the study site every 4 weeks for study assessments and dispensation of the study drug. These visits will occur in the afternoon between 1200-1700 hours at the end of Weeks 4, 8, 12, 24, 36, 48 and 52 (or early termination) and at any time before 1700 hours at the end of Week 16, 20, 28, 32, 40 and 44.

	The study site will call the subjects weekly to remind them to take their study medication daily. Subjects who do not want to continue in the study will be terminated and will be asked to return for an early termination visit approximately 4 weeks after receiving the last dose. Follow-up assessments will be performed at the end of Week 52 (4 weeks after the last dose) or early termination. Efficacy, safety, and pharmacokinetics (PK) will be assessed at scheduled times throughout the study. The treatment period visits (end of Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48) and the follow-up visit (end of Week 52) will have a visit window of ±6 days.
Study Population:	Approximately 180 medically stable adult male and female subjects with clinical diagnoses of schizophrenia or schizoaffective disorder with neuroleptic-induced TD or mood disorder with neuroleptic-induced TD will be enrolled. Of the approximately 180 subjects to be enrolled, approximately 60% may have schizophrenia or schizoaffective disorder. The subjects must be 18 to 85 years of age (inclusive) and have moderate or severe symptoms of TD as assessed by a blinded, external AIMS reviewer, based on the subject's AIMS video recording conducted at screening. Subjects must be psychiatrically stable as determined clinically by the investigator, including a BPRS score of <50 at screening. Approximately 50 subjects who participated in and completed any NBI-98854 Phase 2 study, and were compliant with the study procedures, will be allowed to participate in this study.
Duration of Treatment and Study Participation:	The expected duration of study participation for each subject is approximately 58 weeks, including up to 6 weeks of screening, a 48-week treatment period, and a 4-week follow-up period.
Test Product, Dose, and Mode of Administration:	NBI-98854 will be supplied as capsules containing 40 mg of NBI-98854 ditosylate (dose is of free base). The doses that will be used in this study are: 40 mg qd taken as one NBI-98854 40 mg capsule and 80 mg qd taken as two NBI-98854 40 mg capsules. The subjects will swallow the capsules with at least 4 oz. of water and can take study drug with or without food.
Reference Therapy	Not applicable.

Efficacy Assessments:	The AIMS will be administered and scored by the investigator (or designee) on Day -1 (the day prior to dosing), during the treatment period (end of Weeks 4, 8, 12, 24, 36, and 48), and at the follow-up visit (end of Week 52) or early termination. The AIMS will also be conducted at screening to assess the global severity of TD for study eligibility. At specified timepoints, the AIMS will be video recorded for approximately 10 minutes. The AIMS will be assessed in accordance with the AIMS administration procedure and scoring guidelines provided by the sponsor (or designee). At screening, Day -1, end of Week 8, and at the follow-up visit (end of Week 52) or early termination, the AIMS administration will be video recorded following standardized guidelines and the video recordings will be uploaded to a secure central server. - At screening, a blinded, external AIMS reviewer will access the central server to view the recording and evaluate the subject's global TD severity (based on AIMS item 8) and the investigator (or designee) will score AIMS items 1-12. - On Day -1, at the end of Week 8, and at the follow-up visit (end of Week 52) or early termination, the AIMS recordings will be reviewed by blinded, central AIMS video raters who will score AIMS items 1-7, using a triple-blind consensus scoring process. The CGI-TD will be used to rate the investigator's (or designee's) assessment of the overall global improvement of TD symptoms since initiation of NBI-98854 dosing, and will be administered during the treatment period (end of Weeks 4, 8, 12, 24, 36, and 48) and at the follow-up visit (end of Week 52) or early termination. The Tardive Dyskinesia Impact Scale (TDIS) and Assessment of Most Bothersome Movement in TD (AMBMTD) will be used to evaluate the impairment and disability associated with dyskinesia and to rate the subject's most bothersome movement, respectively. The TDIS and AMBMTD will be completed by the subject at screening, on Day -1 (the day prior to dosing), during the treatment period (end of Weeks 4, 8, 12, 24, 36, and 48), and at the follow-up visit (end of Week 52) or early termination. The Patient Global Impression of Change (PGIC) will be used to evaluate the change in TD symptoms since initiation of the study drug. The PGIC will be completed by the subjects during the treatment period (end of Weeks 4, 8, 12, 24, 36, and 48) and at the follow-up visit (end of Week 52) or early termination.
Plasma Drug Exposure:	Blood samples to evaluate plasma concentrations of NBI-98854, the active metabolite NBI-98782 and possibly other metabolites will be collected during the treatment period (end of Weeks 4, 8, 12, 24, 36, and 48), and at the follow-up visit (end of Week 52) or at early termination.

Safety Assessments:	Safety and tolerability will be monitored throughout the study and will include the following assessments: All subjects: • AEs • Clinical laboratory tests (hematology, clinical chemistry, prolactin, and urinalysis). • Vital signs (including orthostatic blood pressures and pulse) • Physical examinations • 12-lead electrocardiograms (ECGs) • Suicidal ideation and behavior - evaluated using the Columbia-Suicide Severity Rating Scale (C-SSRS) • Drug-induced akathisia and extrapyramidal symptoms – evaluated using the Barnes Akathisia Rating Scale (BARS) and Simpson-Angus Scale (SAS) Specific to underlying disease category: • Depressive symptoms – Calgary Depression Scale for Schizophrenia (CDSS) in subjects who have schizophrenia or schizoaffective disorder and Montgomery-Asberg Depression Rating Scale (MADRS) conducted using the Structured Interview Guide for the MADRS (SIGMA) in subjects who have mood disorder. • Schizophrenia symptoms – Positive and Negative Syndrome Scale (PANSS), only in subjects who have schizophrenia or schizoaffective disorder. • Mania – evaluated using the Young Mania Rating Scale (YMRS) only in subjects who have mood disorder.
Exploratory Assessments:	Plasma samples will be collected for an exploratory assessment of biomarkers associated with the metabolic profile of NBI-98854; however, the data collected will not be reported in this study.
Data Analysis:	Efficacy endpoints as well as safety, PK, and PD data will be summarized by treatment and timepoint (as appropriate) using descriptive statistics. The efficacy measures in this study include the AIMS as scored by the blinded central AIMS video raters, CGI-TD, PGIC, TDIS, and AMBMTD. The AIMS as scored by the investigators (or designee) will be evaluated as an exploratory measure.

2. LIST OF ABBREVIATIONS

AE	Adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	Alanine aminotransferase
AMBMTD	Assessment of Most Bothersome Movement in Tardive Dyskinesia
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration versus time curve
β-hCG	β-human chorionic gonadotropin
BARS	Barnes Akathisia Rating Scale
BMI	Body mass index
BPRS	Brief Psychiatric Rating Scale
CDSS	Calgary Depression Scale for Schizophrenia
CFR	Code of Federal Regulations
CGI-TD	Clinical Global Impression of Change – Tardive Dyskinesia
CK	Creatine kinase
C_{max}	Maximum plasma concentration
CNS	Central nervous system
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	Cytochrome P450
DHTBZ	Dihydrotetrabenazine
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
EC	Ethics committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EPS, EPSE	Extrapyramidal symptoms or side effects
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
HbA1c	Hemoglobin A1c
HBsAg	Hepatitis B surface antigen
HCV-Ab	Hepatitis C virus antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV-Ab	Human immunodeficiency virus antibody
ICF	Informed Consent Form
IRB	Institutional review board
IUD	Intrauterine device

IV	intravenous
IWRS	Interactive Web Response System
K_2EDTA	Dipotassium ethylenediaminetetraacetic acid
MADRS	Montgomery-Asberg Depression Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
MINI	Mini International Neuropsychiatric Interview
NBI	Neurocrine Biosciences, Inc.
NOAEL	No Observed Adverse Effect Level
OTC	Over the counter
PANSS	Positive and Negative Syndrome Scale
PK	Pharmacokinetic(s)
PGIC	Patient Global Impression of Change
QTcF	Fridericia's correction of QT interval
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Simpson-Angus Scale
SD	Standard deviation
SEM	Standard error of the mean
SIGMA	Structured Interview Guide for the Montgomery and Asberg Depression Rating Scale
SST	Serum separator tube
SOC	System organ class
TEAE	Treatment-emergent adverse event
TD	Tardive dyskinesia
TDIS	Tardive Dyskinesia Impact Scale
UBACC	University of California, San Diego Brief Assessment of Capacity to Consent
UDS	Urine drug screen
ULN	Upper limit of normal
US	United States
VMAT2	Vesicular monoamine transporter 2
WBC	White blood cell
YMRS	Young Mania Rating Scale

3. ETHICS

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

- Good Clinical Practice: Consolidated Guideline (International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use, May 1996).
- United States (US) Code of Federal Regulations (CFR) dealing with clinical studies (21 CFR parts 11, 50, 54, 56, 312, and 314).

The ethical requirements of Institutional Review Boards (IRBs)/ Ethics Committees (ECs) and Informed Consent Forms (ICFs) are discussed in Section 13, Regulatory and Ethical Issues

4. INTRODUCTION

4.1. Background

Tardive dyskinesia (TD) is a neurological condition characterized by involuntary movements of the orofacial region (ie, tongue, lips, jaw, face) and choreoathetoid movements in the limbs and trunk. Tardive dyskinesia develops with long-term neuroleptic drug use and often persists after discontinuation of the offending medication. Only a small proportion of patients who are treated with dopamine receptor blocking drugs develop this syndrome. While isolated case reports of TD after short-term exposure exist, most often TD emerges after long-term neuroleptic treatment over months to years. The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) defines chronic exposure (treatment for 3 months or greater) to neuroleptics as the basis for TD diagnosis. In addition to duration and amount of neuroleptic exposure, other risk factors for TD appear to include older age, schizophrenia and cognitive impairment (Margolese et al., 2005). While often of mild intensity, moderate to severe TD can be disabling. Most patients with mild TD are unaware of their involuntary movements and do not seek treatment (Macpherson and Collis, 1992). Severe TD can also cause great bodily harm (eg, lip or tongue lacerations, falls), interference with activities of daily living, and social isolation.

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

Tetrabenazine, a VMAT2 inhibitor and monoamine depletor, was recently approved for the treatment of chorea associated with Huntington's disease. Use of tetrabenazine for the treatment of TD and a variety of hyperkinetic movement disorders has also been described (Ondo et al, 1999; Jankovic and Beach, 1997). The beneficial pharmacologic effects of tetrabenazine on the targeted hyperkinetic involuntary movements have been documented, as well as the adverse effects associated with excessive monoamine reduction, such as sedation, depression, akathisia and parkinsonism. The occurrence of these adverse effects with tetrabenazine have resulted in the need for individualized dosing, dose titration, and management of treatment-related side effects.

The requirement for dose titration with tetrabenazine may be due to its extensive and variable metabolism. Upon absorption, tetrabenazine is rapidly reduced to dihydrotetrabenazine (DHTBZ) which is a mixture of the stereoisomers (±)α-DHTBZ and (±)β-DHTBZ. Since (+)α-DHTBZ is an VMAT2 inhibitor, with potency comparable to tetrabenazine, and since very low exposures of tetrabenazine are observed upon its oral administration, the therapeutic efficacy of tetrabenazine appears to be derived from (+)α-DHTBZ (Kilbourn et al., 1995; Mehvar et al., 1987; Xenazine® Package Insert, 2011). Metabolism of tetrabenazine to (±)α-DHTBZ and (±)β-DHTBZ is highly variable between patients and these stereoisomers of DHTBZ exhibit wide-ranging pharmacology (ie, binding to off-target protein receptors). This represents a source of added risk to the patient and complication for the physician in terms of actively managing a patient's dosing regimen. Orally administered NBI-98854 may provide an advantage by delivering the potent and selective VMAT2 inhibitor (+)α–DHTBZ (NBI-98782), in a consistent and controlled manner minimizing excessive monoamine reduction and off-target effects.

4.2. NBI-98854

NBI-98854 is an orally active valine ester prodrug of a VMAT2 inhibitor (NBI-98782) and is currently under development at Neurocrine Biosciences Inc. (NBI) for the treatment of neuroleptic-induced TD, Tourette Syndrome (TS) and other involuntary movement disorders. NBI-98782 ([+]α–dihydrotetrabenazine) is the most potent and selective of the four stereoisomers of dihydrotetrabenazine formed upon reduction of tetrabenazine (Xenazine® Package Insert, 2011), a Food and Drug Administration (FDA) approved drug for the treatment of Huntington's chorea. NBI-98854 was designed to deliver NBI-98782 in a controlled fashion with reduced peak plasma concentrations and pharmacokinetic (PK) variability that should limit off-target binding and allow for an improved safety profile in human subjects.

The intravenous (IV) and oral PK of NBI-98854 has been studied in mice, rats, monkeys, dogs, and humans. In animals, orally administered NBI-98854 is rapidly absorbed and relatively slowly converted to the active moiety NBI-98782, such that animals are exposed to both the prodrug and the active drug. This is in contrast to other prodrug esters that are typically rapidly absorbed and immediately converted to the active drug. Dose-dependent increases in exposure to both the prodrug and active moiety were seen in animal studies. NBI-98854 appears to cause little or no

cytochrome P450 (CYP) enzyme inhibition or induction at pharmacologically relevant concentrations. Metabolism of NBI-98854 is characterized by esterase-dependent conversion of NBI-98854 to NBI-98782, and CYP3A4/5-dependent mono-oxidation of NBI-98854. The elimination of NBI-98782 is in part catalyzed by CYP2D6. Repeat dose nonclinical toxicology studies conducted in mice, rats, and dogs (up to 9 months duration) have revealed no adverse effects at doses of 60 mg/kg/day in the mouse, 3 mg/kg/day in the rat and 15 mg/kg/day in the dog. Radiolabeled absorption, metabolism, distribution, and excretion studies have confirmed that all abundant human circulating metabolites were identified as circulating metabolites in both rat and dog providing justification for the use of these species for pivotal toxicology studies in the safety assessment of NBI-98854. Additionally, cardiovascular, pulmonary, and CNS safety pharmacology studies have also been conducted, where the no observed adverse effect level (NOAEL) was equal to or exceeded the 15 mg/kg level seen in repeat dose toxicology studies. NBI-98854 had a modest negative effect on rat fertility at 10 mg/kg/day (NOAEL of 3 mg/kg/day). The NOAEL for embryo/fetal development in rats and rabbits was 15 mg/kg/day and 50 mg/kg/day, respectively. There was no evidence of teratogenicity in the rat or rabbits. Finally, NBI-98854 was negative in in vitro mutagenicity assays (namely, Ames and chromosomal aberration) and an in vivo rat micronucleus test.

Twelve clinical studies with NBI-98854 have been completed to date; eight Phase 1 clinical studies in healthy male and female subjects, including elderly, non-elderly, and hepatically impaired adults; and four Phase 2 studies in subjects with TD and a clinical diagnosis of schizophrenia or schizoaffective disorder, mood disorder, or gastrointestinal (GI) disorder. The Phase 1 studies have evaluated the PK of NBI-98854 administered as an oral solution or capsule formulation, pharmacodynamic assessments including serum prolactin and cognitive performance, and safety measures including evaluation of cardiovascular risk using triplicate 12-lead electrocardiogram (ECG) and 24-hour Holter monitoring. The Phase 2 studies have included an evaluation of efficacy in the treatment of symptoms of TD using the Abnormal Involuntary Movement Scale (AIMS).

Clinical PK data indicate that when administered orally under fasted conditions, NBI-98854 appeared to be rapidly absorbed with maximum plasma concentration (C_{max}) being reached within 1 hour. The active metabolite NBI-98782 was formed gradually with maximum plasma concentration being reached 4 to 10 hours after dosing. Plasma concentrations for both NBI-98854 and NBI-98782 appeared to decline after reaching maximal concentration and both exhibited an apparent terminal half-life of approximately 20 hours in non-elderly adult subjects and 23 to 28 hours in elderly subjects. Preliminary data from healthy volunteer studies suggest that coadministration of NBI-98854 with strong CYP3A4 and CYP2D6 inhibitors is expected to increase the C_{max} and area under the plasma concentration versus time curve (AUC) of NBI-98782 by approximately 2-fold. A similar approximately 2-fold increase in NBI-98782 was observed when NBI-98854 is given to subjects with moderate or severe hepatic impairment.

NBI-98854 has been generally well tolerated in single doses up to 300 mg and in multiple doses of up to 100 mg. Treatment-emergent adverse events (TEAEs) consistent with the pharmacological effects of monoamine reduction (eg, fatigue, insomnia, nervousness) occurred at a lower incidence in the NBI-98854 100 mg dose compared to the 50 mg dose in the Phase 2 studies. Most TEAEs were transient and considered mild or moderate in intensity. Thirteen treatment-emergent serious adverse events (SAEs) among 10 subjects have been reported. No SAEs have been assessed by the investigator as possibly related to study drug. No cardiovascular, laboratory, or vital sign-related safety signals have been identified. Increases in serum prolactin above normal laboratory ranges have been noted, but there have been no TEAEs associated with hyperprolactinemia. In general, depression, drug-induced akathisia, and drug induced parkinsonism did not worsen during treatment with NBI-98854.

Results from a small, open-label Phase 2 study in 6 subjects with schizophrenia or schizoaffective disorder and TD indicated improvement in abnormal involuntary movements as measured by the AIMS after 12 consecutive days of NBI-98854 dosing (4 days each at 12.5 mg, 25 mg, and 50 mg). Findings from a second Phase 2 study conducted in this patient population, a placebo-controlled crossover study in 37 subjects, indicated a greater improvement in the AIMS score after 14 days of treatment with NBI-98854 50 mg compared to placebo. Preliminary results from two more recently completed Phase 2b studies indicated an improvement in the AIMS score after 6 weeks of continuous dosing with either NBI-98854 50 mg once daily, continuous dosing at NBI-98854 100 mg once daily for 2 weeks followed by continuous dosing at NBI-98854 50 mg once daily for 4 weeks (NBI-98854-1201) or 6 weeks of titrated doses from 25 mg up to 75 mg NBI-98854 once daily (NBI-98854-1202). Preliminary results from an open-label safety extension with dosing out to 12 weeks (NBI-98854-1201) continued to show benefit in subjects continuing on with NBI-98854 50 mg daily dosing and also in subjects originally assigned to placebo who went on to receive NBI-98854 50 mg once daily for the 6 weeks of open-label treatment period. Results from the 6-week dose-titration study (NBI-98854-1202) showed a statistically significant reduction in the AIMS dyskinesia total score in the NBI-98854 group compared to placebo. A statistically significant higher responder rate (ie, ≥50% improvement in AIMS dyskinesia total score from baseline) was also observed in the NBI-98854 group compared to placebo.

4.3. Study Rationale and Selection of Dose

The present study is a Phase 3, open-label, fixed-dose titration study of NBI-98854 (titrated from 40 mg to 80 mg) in medically stable subjects with schizophrenia or schizoaffective disorder or mood disorder and TD. Subjects will be required to have moderate or severe TD as determined by a blinded, external AIMS reviewer to assure appropriate subject inclusion. This study is designed to evaluate the safety and tolerability of NBI-98854 administered for up to 48 weeks for the treatment of TD.

In the current study, all subjects will receive NBI-98854 for 48 weeks. Subjects will receive a starting dose of NBI-98854 40 mg once daily for 4 weeks. After 4 weeks,

subjects may be eligible for a dose escalation to NBI-98854 80 mg provided that (1) the investigator or designee's assessment of the subject's Clinical Global Impression of Change – Tardive Dyskinesia (CGI-TD) is "minimally improved", "not changed", "minimally worse", "much worse" or "very much worse", and (2) the safety and tolerability of the current dose is acceptable as determined by a physician. The investigator will increase the dose for any subject meeting both criteria and may decrease the dose to the previous dose at any time for a subject who is unable to tolerate the dose increase; subjects who have had a dose reduction will continue at that dose until the end of Week 48 (refer to the schematic in Section 16.2). Subjects will be discontinued from the study if they are unable to tolerate the starting dose (40 mg), or resumption of the starting dose. This fixed dose titration design, based on Phase 2 data, maximizes the proportion of subjects receiving an adequate dose for robust clinical response (eg, ≥50% reduction in dyskinesia) along with good tolerability. It is anticipated that approximately 30% of subjects will complete on the 40 mg dose and approximately 70% of subjects on the 80 mg dose.

Rationale for Dose Selection

Clinical data from TD subjects administered repeated doses of NBI-98854 from 12.5 mg to 100 mg per day indicate that NBI-98854 is generally well tolerated and associated with dose-related efficacy. Exposure-response analysis indicates that a steady state C_{max} of 20 to 40 ng/mL NBI-98782 is an appropriate plasma concentration range for efficacy.

NBI-98854 doses of 40 mg and 80 mg are associated with exposure to the active metabolite, NBI-98782, in the target range of 20 to 40 ng/mL when administered initially as 40 mg once daily and adjusted upward to 80 mg if dyskinesia persists after several weeks of treatment. These doses have been selected as a simple and practical method to provide exposure associated with acceptable tolerability and robust efficacy. Doses below 40 mg are well tolerated but offer dyskinesia reduction comparable to placebo. Doses above 80 mg afford little incremental benefit but increase the risk of adverse events (AEs) reflecting extension of VMAT2 pharmacology. Because many patient-specific factors appear to influence tolerability and efficacy, clinicians would be guided to start all patients at the lower of two doses. Preliminary analysis of Phase 2 data suggests that these patient-specific factors include body weight, CYP2D6 genotype, concomitant medications, comorbid medical conditions and a number of other clinical variables.

5. STUDY OBJECTIVES

The objective of this study is to evaluate the safety and tolerability of NBI-98854 (titrated from 40 mg to 80 mg) administered once daily for up to 48 weeks.

6. OVERVIEW OF STUDY DESIGN

Subjects will provide written informed consent before any study-related procedures, including washout of disallowed medications, are performed as described in Section 6.1.

6.1. Study Design

This is a Phase 3, open-label, dose-titration study to evaluate the safety and tolerability of NBI-98854 (titrated from 40 mg to 80 mg) administered once daily (qd) for a total of 48 weeks of treatment. Approximately 180 medically stable male and female subjects with clinical diagnoses of schizophrenia or schizoaffective disorder with neuroleptic induced TD or mood disorder with neuroleptic induced TD will be enrolled. Of the approximately 180 subjects, approximately 60% may have schizophrenia or schizoaffective disorder.

All subjects must sign an ICF prior to the conduct of any study related procedures, including washout of medications disallowed in the study. 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). A copy of the UBACC is located in Appendix 17.1. During the initial step of consent process, the ICF will be reviewed with the subject. The UBACC will then be administered. Only subjects who are deemed to have the capacity to provide consent may sign the ICF. Subjects may also be asked to sign an optional release form to allow their AIMS video recordings to be used for educational purposes. After providing informed consent, the subjects will be screened for eligibility for up to 6 weeks prior to Day -1 (baseline visit) (Week -6 to Day -1).

On Day -1, eligible subjects will receive a supply of NBI-98854 40 mg qd for the first 4 weeks of the treatment period. Beginning on Day 1, study drug will be self-administered at home (in the presence of their caregiver, if applicable) in the morning between 0700 and 1000 hours.

At the end of Week 4, the investigator may escalate the subject's dose to 80 mg or continue with the subject's current dose. A dose escalation will be allowed at the end of Week 4 if (1) the investigator or designee's assessment of the CGI-TD is "minimally improved", "not changed", "minimally worse", "much worse", or "very much worse", and (2) the safety and tolerability of the current dose is acceptable as determined by a physician. The subject will then continue at the 80 mg dose until the end of the treatment period (end of Week 48).

At any time after a dose escalation, the investigator may decrease the dose to 40 mg if the subject is unable to tolerate the dose increase. The subject will then continue at the 40 mg dose until the end of the treatment period (end of Week 48). Subjects who are unable to tolerate the starting dose of 40 mg, or the resumption of 40 mg, will be discontinued from the study (refer to the schematic in Section 16.2).

Subjects will return to the study site every 4 weeks in the afternoon for study assessments and dispensation of the study drug. These visits will occur in the afternoon between 1200-1700 hours at the end of Weeks 4, 8, 12, 24, 36, 48 and 52 (or early termination) and at any time before 1700 hours at the end of Week 16, 20, 28, 32, 40 and 44. The study site will call subjects weekly to remind them to take their study medication daily. Subjects who do not want to continue in the study will be terminated and will be asked to return for an early termination visit approximately 4 weeks after receiving the last dose. Follow-up assessments will be performed at the end of Week 52 (4 weeks after the last dose) or early termination.

Efficacy, safety, and PK will be assessed at scheduled times throughout the study. The treatment period visits (end of Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48) and the follow-up visit (end of Week 52) will have a visit window of ±6 days.

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

6.1.1. Efficacy, Blood Sample Collections, and Safety Assessments for All Subjects

Efficacy assessments will be performed using the AIMS, the CGI-TD, the Patient Global Impression of Change (PGIC), the Tardive Dyskinesia Impact Scale (TDIS), and the Assessment of Most Bothersome Movement in Tardive Dyskinesia (AMBMTD). The AIMS will be administered at screening, on Day -1 (the day prior to dosing), during the treatment period (end of Weeks 4, 8, 12, 24, 36, and 48), and at the follow-up visit (end of Week 52) or early termination. The AIMS will be administered and scored by the investigator (or designee) in accordance with the AIMS administration procedure and scoring guidelines provided by the sponsor (or designee). At screening, Day -1, end of Week 8, and at the follow-up visit (end of Week 52) or early termination, the AIMS assessment will be video recorded (approximately 10 minutes) following standardized guidelines and the video recording will be uploaded to a secure central server. At screening, a blinded, external AIMS reviewer will access the central server to view the recoding and evaluate the subject's global TD severity (based on AIMS item 8). The subject must have moderate or severe TD as determined by the blinded, external reviewer to be eligible for study participation. The investigator or designee will score AIMS items 1-10 and complete AIMS items 11-12. The AIMS video recording conducted on Day -1, at the end of Week 8, and at the follow-up visit (end of Week 52) or early termination will be reviewed by blinded, central AIMS video raters who will score AIMS items 1-7 using a triple-blind consensus scoring process. Refer to Sections 8.3.1.1, 8.3.1.2 and 8.3.1.3 for details.

The CGI-TD will be used to rate the investigator or designee's assessment of the overall global improvement of TD symptoms since initiation of study drug dosing, and will be administered during the treatment period (end of Weeks 4, 8, 12, 24, 36, and 48) and at the follow-up visit (end of Week 52) or early termination.

The PGIC will be used to evaluate the change in TD symptoms since initiation of study drug dosing, and will be completed by the subjects during the treatment period (end of

Weeks 4, 8, 12, 24, 36, and 48) and at the follow-up visit (end of Week 52) or early termination.

A patient reported outcome, the TDIS and AMBMTD will be used to assess the impairment and disability associated with dyskinesia and to rate the subject's most bothersome movement, respectively. The TDIS will be completed by the subjects at screening, on Day -1 (the day prior to dosing), during the treatment period (end of Weeks 4, 8, 12, 24, 36, and 48), and at the follow-up visit (end of Week 52) or at early termination.

The Brief Psychiatric Rating Scale (BPRS) will be performed at screening as an assessment of the severity of psychopathology to determine study eligibility.

Blood samples for plasma drug concentration analysis will be collected during the study. A blood sample will be collected from enrolled subjects on Day -1 and analyzed to determine CYP2D6 status. Plasma samples for an exploratory assessment of biomarkers associated with the metabolic profile of NBI-98854 will be collected during the study.

Safety and tolerability assessments including AE monitoring, clinical laboratory tests (including hematology, clinical chemistry, prolactin, and urinalysis), vital sign measurements, PE, and 12-lead ECG will be conducted at scheduled times throughout the study. Suicidal ideation and behavior will be evaluated using the Columbia-Suicide Severity Rating Scale (C-SSRS). The Barnes Akathisia Rating Scale (BARS) and the Simpson-Angus Scale (SAS) will be used to assess the presence and severity of drug-induced akathisia and drug-induced extrapyramidal symptoms, respectively.

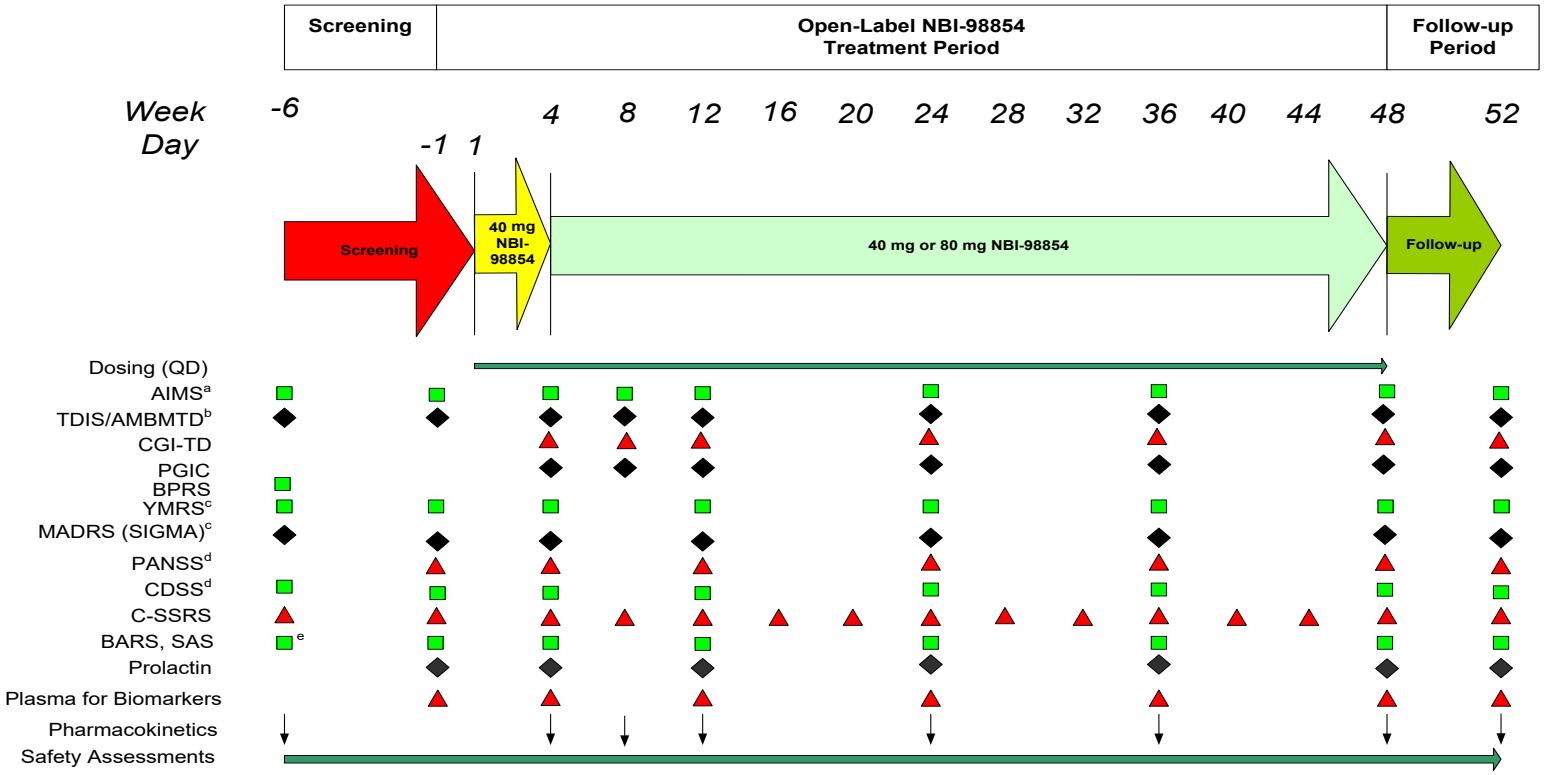
6.1.2. Additional Safety Assessments for Subjects with Schizophrenia or Schizoaffective Disorder:

Depressive symptoms will be evaluated using the Calgary Depression Scale for Schizophrenia (CDSS). Psychiatric symptoms will be assessed using the Positive and Negative Syndrome Scale (PANSS).

6.1.3. Additional Safety Assessments for Subjects with Mood Disorder:

The Young Mania Rating Scale (YMRS) will be used to assess manic symptoms. Depressive symptoms will be evaluated with the Montgomery-Asberg Depression Rating Scale (MADRS) conducted using the Structured Interview Guide for MADRS (SIGMA).

Figure 1. Study Design Schematic



AIMS = Abnormal Involuntary Movement Scale; AMBMTD = Assessment of Most Bothersome Movement in Tardive Dyskinesia; BARS = Barnes Akathisia Rating Scale; BPRS = Brief Psychiatric Rating Scale; CDSS = Columbia Depression Scale for Schizophrenia; CGI-TD = Clinical Global Impression - Tardive Dyskinesia; C-SSRS = Columbia Suicide Severity Rating Scale; MADRS (SIGMA) = Montgomery-Asberg Depression Rating Scale using the Structured Interview Guide for the MADRS; PANSS = Positive and Negative Syndrome Scale; PGIC = Patient Global Impression of Change; QD = once daily; SAS = Simpson-Angus Scale; TDIS = Tardive Dyskinesia Impact Scale; YMRS = Young Mania Rating Scale

a AIMS will be administered and scored by the investigator (or designee). At screening, Day -1, end of Week 8, and at the follow-up visit (end of Week 52) or early termination, the AIMS will be video recorded for approximately 10 minutes. At screening, a blinded, external AIMS reviewer will evaluate the severity of TD symptoms; eligible subjects must have moderate or severe symptoms of TD.
b The TDIS and AMBMTD will be completed by the subject.
c Assessments for subjects with Mood Disorder only.
d Assessments for subjects with Schizophrenia or Schizoaffective Disorder only.
e At Screening, only SAS will be administered.

7. STUDY POPULATION

This study will be conducted in approximately 180 medically stable adult male or female subjects with clinical diagnoses of schizophrenia or schizoaffective disorder with neuroleptic induced TD or mood disorder with neuroleptic induced TD. Of the approximately 180 subjects to be enrolled, approximately 60% may have schizophrenia or schizoaffective disorder. Subjects must have moderate to severe TD as assessed at screening by a blinded external reviewer. Approximately 50 subjects who participated in and completed any NBI-98854 Phase 2 study, and were compliant with the study procedures, will be allowed to participate in this study. Subjects must meet all the inclusion criteria and none of the exclusion criteria in order to qualify for the study.

7.1. Inclusion Criteria

To participate in this study, subjects must:

1. Be male or female, aged 18 to 85 years (both inclusive).
2. Subjects of childbearing potential must agree to use hormonal or two forms of nonhormonal contraception (dual contraception) consistently during the screening, treatment and follow-up periods of the study.

   Acceptable methods of contraception include the following:

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

   The following subjects are not required to use contraception:

   - Subjects who practice total abstinence from sexual intercourse as the preferred lifestyle (periodic abstinence is not acceptable).
   - Female subjects with partners or male subjects who had been vasectomized at least 3 months prior to screening.
   - Female subjects who have been postmenopausal for at least 1 year prior to screening.
   - Female subjects who are surgically sterile (ie, bilateral oophorectomy, hysterectomy or bilateral tubal ligation) at least 3 months prior to screening.
3. Female subjects who have not been postmenopausal for at least 1 year must have a negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test at screening and a urine pregnancy test on Day -1.

4. Have one of the following clinical diagnoses for at least 3 months prior to screening:

   - Schizophrenia or Schizoaffective Disorder as defined in the in the Diagnostic and Statistical Manual of Mental Disorders, (DSM, eg, DSM-IV).
   - Mood Disorder as defined in the DSM (eg, DSM-IV).

   This criterion will be satisfied if the subject is able to provide a medical record of the diagnosis or reliable self-reported medical history and medications taken for the disorder. If the subject is unable to provide a medical record or reliable self-reported medical record, the investigator must confirm the psychiatric diagnosis based on an evaluation using the Mini International Neuropsychiatric Interview (MINI) (applicable module must be used to assess underlying disease).

5. Have a clinical diagnosis of neuroleptic-induced TD as defined in the DSM (eg, DSM-IV code 333.82; refer to Section 16.1) for at least 3 months prior to screening. This criterion will be satisfied if the subject is able to provide a medical record of the TD diagnosis or the investigator can confirm the TD diagnosis based on physical examination, and reliable self-reported medical history and medication use that show evidence of involuntary movements associated with dopamine antagonist/antipsychotic medication exposure that are clearly distinct from the typical parkinsonism associated with extrapyramidal symptoms or side effects (EPS or EPSE).

6. Have moderate or severe TD (AIMS Item 8, severity of abnormal movement overall) as assessed by a blinded, external AIMS reviewer using a video recording of the subject's AIMS assessment administered at the study site by the investigator (or designee) at screening.

7. Maintenance medication(s) for schizophrenia or schizoaffective disorder, mood disorders, and other protocol allowed concurrent medications should be at a stable dose (including no changes to the dose and frequency of ongoing medications and no discontinuation of medications for a minimum of 30 days before screening). Exceptions may be allowed if discussed with and approved by NBI's medical monitor (or designee) prior to Day -1. If an exception is approved, the subject must be on a stable dose for 30 days prior to Day -1. Benzodiazepines must be at a stable dose for 2 weeks before screening. This criterion will be satisfied if the investigator can confirm prior and current medications and doses through reliable subject-reported information (eg, subject provides a list of medications and doses).

8. Subjects with a diagnosis of schizophrenia or schizoaffective disorder who are not using antipsychotic medication must have a stable psychiatric status as clinically determined by the investigator. Subjects with a diagnosis of bipolar disorder must be on stable dose of mood stabilizer(s) (eg, lithium, valproate, olanzapine) for a minimum of 30 days before screening. Exceptions may be allowed as mentioned in inclusion criterion #7. The use of carbamazepine is permitted if discussed with and approved by NBI's medical monitor (or designee) prior to Day -1.

9. Be in good general health and expected to complete the clinical study as designed.

10. Have a body mass index (BMI) of 18 to 38 kg/m^2 (inclusive) at screening. Subjects with BMI that is out of the specified range will require discussion with and approval by NBI's medical monitor (or designee) prior to Day -1. (BMI is defined as the subject's weight in kg divided by the square of the subject's height in meters).
11. Have adequate hearing, vision, and language skills to perform the procedures specified in the protocol.
12. Have voluntarily provided informed consent and have signed an ICF indicating that the purpose of the study has been explained, and are willing and able to adhere to the study regimen and study procedures described in the ICF. Subjects must also have been deemed capable of providing consent to study participation using the UBACC prior to signing the ICF.
13. Have a negative urine drug screen (UDS) (negative for amphetamines, barbiturates, benzodiazepine, phencyclidine, cocaine, opiates, or cannabinoids) at screening (central laboratory results) and Day -1 (UDS kit results conducted at the study site) except for any subject receiving a stable dose of benzodiazepines or opiates. Subjects with positive cannabinoid results may be allowed to participate in the study provided that the subject is given thorough counseling and agrees to refrain from using cannabinoids for the duration of his/her study participation.
14. Have a negative alcohol breath test at screening and Day -1.
15. Be willing to provide authorization for access to personal health information in conjunction with US Health Insurance Portability and Accountability Act (HIPAA).

7.2. Exclusion Criteria

7.2.1. Exclusion Criteria for All Subjects

Subjects will be excluded from the study if they:

1. Have an active, clinically significant unstable medical condition within 1 month (30 days) prior to screening.
2. Have comorbid abnormal involuntary movement(s) (eg, parkinsonism, akathisia, truncal dystonia) that is more prominent than TD as assessed by a blinded, external AIMS reviewer using video recording of the AIMS administration at screening.
3. Have a SAS score ≥3 on two or more items at screening or Day -1, excluding Items 8 and 10.
4. Have a known history of substance dependence or substance (drug) or alcohol abuse within the 3 months before Day -1 (nicotine and caffeine dependence are not exclusionary), as defined in the DSM (eg, DSM-IV).
5. Have BPRS total score of ≥50 at screening.
6. Have a significant risk of suicidal or violent behavior. Subjects with any suicidal behavior or suicidal ideation of type 4 (active suicidal ideation with some intent to act, without specific plan) or type 5 (active suicidal ideation with specific plan and

intent) based on the C-SSRS in the 3 months before screening (using Baseline/Screening version) and on Day -1 (using Since Last Visit version) will be excluded.

7. Have a known history of neuroleptic malignant syndrome.
8. Have a known history of long QT syndrome or cardiac tachy-arrhythmia.
9. Have a screening or Day -1 average triplicate ECG QT interval corrected for heart rate using Fridericia's correction of QT interval (QTcF) of >450 msec (males) or >470 msec (females) or the presence of any clinically significant cardiac abnormality.
10. Receive any excluded concomitant medication (refer to Section 8.9.1); subjects receiving medications known to prolong the QT interval must be discussed with and approved by NBI's medical monitor (or designee) on a case-by-case basis prior to Day -1.
11. Have any of the following laboratory test abnormalities at screening:
    - serum creatinine >1.5 times upper limit of normal (ULN).
    - Aspartate aminotransferase (AST) ≥2.5 times ULN.
    - Alanine aminotransferase (ALT) ≥2.5 times ULN.
    - Gamma-glutamyl transferase (GGT) ≥3.0 times ULN. Subjects with GGT ≥3.0 times ULN will require discussion with and approval by NBI's medical monitor or designee prior to Day -1 in order to participate in the study.
    - Total bilirubin >1.5 mg/dL.
12. Have a hematologic malignancy or solid tumor diagnosed within 3 years prior to screening, with the exception of localized skin cancer or carcinoma in situ of the cervix.
13. Have any of the following hematologic abnormalities at screening:
    - hemoglobin <10 g/dL.
    - white blood cell (WBC) count <3.0 x 10^3/mm^3.
    - platelet count <100,000/mm^3.
14. Have other biochemistry or hematology results not within the laboratory's reference range and deemed by the investigator to be clinically significant.
15. Have a positive human immunodeficiency virus antibody (HIV-Ab) test result or hepatitis B surface antigen (HBsAg) test result at screening. Subject with positive hepatitis C virus antibody (HCV-Ab) and confirmatory positive polymerase chain reaction (PCR) reflex test results at screening will be allowed to participate in the study provided that the subject is asymptomatic as assessed by the investigator and does not meet the liver function tests abnormalities (ALT, AST, GGT, and total bilirubin) exclusionary criterion #11.
16. Have received an investigational drug within 30 days before screening or plan to use an investigational drug (other than NBI-98854) during the study.

17. Have a blood loss ≥550 mL or donated blood within 30 days before Day -1.
18. Have an allergy, hypersensitivity, or intolerance to tetrabenazine.
19. Are currently participating or had participated in the NBI-98854-1304 study.
20. Are currently pregnant or breastfeeding.

7.2.2. Exclusion Criteria for Subjects with Clinical Diagnosis of Schizophrenia or Schizoaffective Disorder

In addition to the exclusion criteria for all subjects, the following criteria must not be met for subjects with schizophrenia or schizoaffective disorder.

21. Have CDSS total score of ≥10 at screening or Day -1.
22. Have a PANSS total score of ≥70 at Day -1.

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

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

23. Have YMRS total score of >10 at screening or Day -1.
24. Have been hospitalized for bipolar disorder or major depressive disorder within 6 months of screening.
25. Have had mood episodes (hypomania, mania, depressive, etc.) within 2 months of screening and Day -1.
26. Have history of rapid cycling (>4 mood episodes per year) or ultra-rapid (>4 mood episodes per month).
27. Have MADRS (SIGMA) total score of >13 at screening or Day -1.

7.3. Subject Identification and Replacement

Subjects will be identified by their unique subject number (combination of site number and subject number) and initials (first, middle, last). Subject initials and subject number will be noted on the electronic case report forms (eCRFs), laboratory documents, and ECG tracings. Subjects who discontinue the study will not be replaced.

7.4. Randomization

Subjects will not be randomized in this study.

8. STUDY EVALUATIONS

8.1. Schedule of Assessments

Schedules of assessments that summarize the frequency and timing of all assessments for subjects with schizophrenia or schizoaffective disorder or subjects with mood disorders are provided in Table 1 and Table 2, respectively. No protocol-related procedures, including the cessation of prohibited concomitant medications, should be

performed before subjects provide written informed consent. Subject-related events and activities including specific procedures, concomitant medications, dispensing of study drug, and descriptions of AEs should be recorded in the appropriate source documents and eCRFs.

Table 1. Schedule of Assessments for Subjects with Schizophrenia or Schizoaffective Disorder

Procedure[a]	Screening Period	Baseline	Open-Label NBI-98854 Treatment Period												Follow-up / ET
Week[b]	-6 TO -1	DAY -1	4	8	12	16	20	24	28	32	36	40	44	48	52[c]
Visit[b]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Informed consent / UBACC	X														
Inclusion/exclusion criteria	X	UPDATE													
Medical history	X	UPDATE													
Physical examination (including weight)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X														
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test[e]	X (S)	X (S,U)	X (U)	X (U)	X (U)	X (U)	X (U)	X (U)	X (U)	X (U)	X (U)	X (U)	X (U)	X (U)	X (U)
Serology (HBsAg, HCV-Ab and HIV-Ab)	X														
Clinical laboratory tests[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine drug screen[g]	X	X													
Alcohol breath test	X	X													
Genotype blood sample		X													
Serum prolactin		X	X		X			X			X			X	X
Plasma for biomarkers		X	X		X			X			X			X	X
PK plasma sample[h]			X	X	X			X			X			X	X
AIMS[i]	X	X	X	X	X			X			X			X	X
TDIS and AMBMTD[j]	X	X	X	X	X			X			X			X	X
CGI-TD			X	X	X			X			X			X	X
PGIC			X	X	X			X			X			X	X
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BPRS	X														
BARS		X	X		X			X			X			X	X
SAS	X	X	X		X			X			X			X	X
CDSS	X	X	X		X			X			X			X	X
PANSS		X	X		X			X			X			X	X
NBI-98854 dosing at home[k]			X	X	X	X	X	X	X	X	X	X	X	X	
Dispense NBI-98854[l]		X	X	X	X	X	X	X	X	X	X	X	X		
NBI-98854 accountability[m]			X	X	X	X	X	X	X	X	X	X	X	X	
AE monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior and concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Outpatient clinic visits	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations and footnotes appear on the next page.

Definitions: AE=adverse event; AIMS=Abnormal Involuntary Movement Scale; AMBMTD=Assessment of Most Bothersome Movement in Tardive Dyskinesia; BARS=Barnes Akathisia Rating Scale; BPRS=Brief Psychiatric Rating Scale; CDSS=Calgary Depression Scale for Schizophrenia; CGI-TD=Clinical Global Impression-Tardive Dyskinesia; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ET=early termination; HBsAg=hepatitis B surface antigen; HCV-Ab=hepatitis C virus antibody; HIV-Ab=human immnunodeficiency virus antibody; PANSS=Positive and Negative Syndrome Scale; PGIC=Patient Global Impression of Change; PK=pharmacokinetic; s=serum; SAS=Simpson-Angus Scale; TDIS=Tardive Dyskinesia Impact Scale; u=urine; UBACC=University of California, San Diego Brief Assessment of Capacity to Consent.

a. Study assessments will be conducted at approximately the same time in the afternoon (between 1200-1700 hours) at screening, Day -1, at the end of Weeks 4, 8, 12, 24, 36, 48 and 52 (or early termination) and at any time before 1700 hours at the end of Week 16, 20, 28, 32, 40 and 44.
b. Day -1 visit is the day of baseline assessments. Day 1 is the first day of dosing; NBI-98854 will be self-administered at home and subjects are not required to come to the study site. The study visits after Day -1 will have a visit window of ±6 days.
c. Final study visit for subjects who complete the study (or early termination).
d. A standard 12-lead ECG will be conducted after the subject has rested supine for at least 5 minutes. The ECG parameters that will be assessed include HR, QT, QTcF, and PR intervals, and QRS duration based on the ECG machine readings (QTcF may be calculated).
e. Pregnancy tests are only required for women who are not postmenopausal for at least 1 year prior to screening. Serum pregnancy tests will be conducted at screening and Day -1. A urine pregnancy test will be conducted at Day -1 and all subsequent visits. The urine pregnancy test result on Day -1 will be used to confirm eligibility.
f. Clinical laboratory tests include hematology, chemistry and urinalysis. All blood samples will be obtained under non-fasted conditions.
g. Urine drug screen will be analyzed at Screening and Day -1 by the central lab. In addition, a UDS kit provided by the central lab will used at the site to confirm eligibility on Day -1.
h. Subjects will be asked to record and provide dosing times on the days during the treatment period when blood PK samples are collected.
i. The AIMS will be administered and scored at the site by the investigator (or designee). The AIMS will be video recorded for approximately 10 minutes at screening, Day -1, end of Week 8, and at the follow-up visit (end of Week 52 or early termination). At screening, a blinded AIMS reviewer will view the video and evaluate the TD symptom severity (see inclusion #6) to determine subject eligibility.
j. TDIS and AMBMTD will be completed by the subjects.
k. Subjects will self-administer NBI-98854 daily (in the morning at approximately the same time) at home in the presence of their caregiver (if applicable). Subject or caregiver will record daily the date and time of dosing on the drug packaging form provided. A representative from the study site will call the subjects weekly to remind them to take NBI-98854 daily.
l. Subjects will receive a 4-week supply (two kits) of NBI-98854 at Day -1 and will need to return to study site every 4 weeks to obtain a 4-week supply of NBI-98854.
m. At the end of Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, and 44 subjects will return all used and unused NBI-98854, and a compliance check will be performed by counting the capsules returned at the visit.

Table 2. Schedule of Assessments for Subjects with Mood Disorders

Procedure[a]	Screening Period	Baseline	Open-Label NBI-98854 Treatment Period												Follow-up / ET
Week[b]	**-6 TO -1**	**DAY -1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52[c]**
Visit[b]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Informed consent / UBACC	X														
Inclusion/exclusion criteria	X	UPDATE													
Medical history	X	UPDATE													
Physical examination (including weight)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X														
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test[e]	X (S)	X (S,U)	X (U)	X (U)	X (U)	X (U)	X (U)	X (U)	X (U)	X (U)	X (U)	X (U)	X (U)	X (U)	X (U)
Serology (HBsAg, HCV-Ab and HIV-Ab)	X														
Clinical laboratory tests[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine drug screen[g]	X	X													
Alcohol breath test	X	X													
Genotype blood sample		X													
Serum prolactin		X	X		X			X			X			X	X
Plasma for biomarkers		X	X		X			X			X			X	X
PK plasma sample[h]			X	X	X			X			X			X	X
AIMS[i]	X	X	X	X	X			X			X			X	X
TDIS and AMBMTD[j]	X	X	X	X	X			X			X			X	X
CGI-TD			X	X	X			X			X			X	X
PGIC			X	X	X			X			X			X	X
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BPRS	X														
BARS		X	X		X			X			X			X	X
SAS	X	X	X		X			X			X			X	X
MADRS (SIGMA)	X	X	X		X			X			X			X	X
YMRS	X	X	X		X			X			X			X	X
NBI-98854 dosing at home[k]			X	X	X	X	X	X	X	X	X	X	X	X	
Dispense NBI-98854[l]		X	X	X	X	X	X	X	X	X	X	X	X		
NBI-98854 accountability[m]			X	X	X	X	X	X	X	X	X	X	X	X	
AE monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior and concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Outpatient clinic visits	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations and footnotes appear on the next page.

Definitions: AE=adverse event; AIMS=Abnormal Involuntary Movement Scale; AMBMTD=Assessment of Most Bothersome Movement in Tardive Dyskinesia; BARS=Barnes Akathisia Rating Scale; BPRS=Brief Psychiatric Rating Scale; CGI-TD=Clinical Global Impression-Tardive Dyskinesia; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=Electrocardiogram; ET=Early Termination; HBsAg=Hepatitis B Surface Antigen; HCV-Ab=Hepatitis C Virus Antibody; HIV-Ab=Human Immnunodeficiency Virus Antibody; MADRS (SIGMA)=Montgomery-Asberg Depression Rating Scale using the Structured Interview Guide for the MADRS; PGIC=Patient Global Impression of Chance; PK=Pharmacokinetic; s=serum; SAS=Simpson-Angus Scale; TDIS=Tardive Dyskinesia Impact Scale; u=urine; UBACC=University of California, San Diego Brief Assessment of Capacity to Consent; YMRS=Young Mania Rating Scale.

a. Study assessments will be conducted at approximately the same time in the afternoon (between 1200-1700 hours) at screening, Day -1, at the end of Weeks 4, 8, 12, 24, 36, 48 and 52 (or early termination) and at any time before 1700 hours at the end of Week 16, 20, 28, 32, 40 and 44.
b. Day -1 visit is the day of baseline assessments. Day 1 is the first day of dosing; NBI-98854 will be self-administered at home and subjects are not required to come to the study site. The study visits after Day -1 will have a visit window of ±6 days.
c. Final study visit for subjects who complete the study (or early termination).
d. A standard 12-lead ECG will be conducted after the subject has rested supine for at least 5 minutes. The ECG parameters that will be assessed include HR, QT, QTcF, and PR intervals, and QRS duration based on the ECG machine readings (QTcF may be calculated).
e. Pregnancy tests are only required for women who are not postmenopausal for at least 1 year prior to screening. Serum pregnancy tests will be conducted at screening and Day -1. A urine pregnancy test will be conducted at Day -1 and all subsequent visits. The urine pregnancy test result on Day -1 will be used to confirm eligibility.
f. Clinical laboratory tests include hematology, chemistry and urinalysis. All blood samples will be obtained under non-fasted conditions.
g. Urine drug screen will be analyzed at Screening and Day -1 by the central lab. In addition, a UDS kit provided by the central lab will used at the site to confirm eligibility on Day -1.
h. Subjects will be asked to record and provide dosing times on the days during the treatment period when blood PK samples are collected.
i. The AIMS administered and scored at the site by the investigator (or designee). At screening, Day -1, end of Week 8, and t the follow-up visit (end of Week 52 or early termination), the AIMS will be video recorded for approximately 10 minutes. At screening, a blinded AIMS reviewer will view the video and evaluate the TD symptom severity (see inclusion #6) to determine subject eligibility.
j. TDIS and AMBMTD will be completed by the subjects.
k. Subjects will self-administer NBI-98854 daily (in the morning at approximately the same time) at home in the presence of their caregiver (if applicable). Subject or caregiver will record daily the date and time of dosing on the drug packaging form provided. A representative from the study site will call the subjects weekly to remind them to take their study medication daily.
l. Subjects will receive a 4-week supply (two kits) of NBI-98854 at Day -1 and will need to return to study site every 4 weeks to obtain a 4-week supply of NBI-98854.
m. At the end of Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, and 44 subjects will return all used and unused NBI-98854, and a compliance check will be performed by counting the capsules returned at the visit.

8.2. Screening Assessment

8.2.1. Brief Psychiatric Rating Scale (BPRS)

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

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

The investigator or other qualified site personnel will administer and score the scale at screening, and subjects must have a BPRS total score <50 to be eligible for study participation (see exclusion criterion #5). A copy of the BPRS is provided in Appendix 17.2.

8.3. Efficacy Assessments

8.3.1. Abnormal Involuntary Movements Scale (AIMS)

The severity of TD will be assessed using the AIMS rating scale. This scale was developed by the Psychopharmacology Research Branch of the National Institute of Mental Health (Guy, 1976a). The AIMS rates a total of 10 items with 9 items rating involuntary movement from 0 (no dyskinesia) to 4 (severe dyskinesia). Items 1 through 7 include facial and oral movements (Items 1-4), extremity movements (Items 5-6), and trunk movements (Item 7). The AIMS dyskinesia total score for Items 1-7 ranges from 0 to 28; a higher score reflects increased severity. Items 8, 9 and 10 rate global judgments with item 10 being rated based only on subject's report of his/her awareness of abnormal movements from 0 (no awareness) to 4 (aware, severe distress). Items 11-12 are yes-no questions concerning problems with teeth and/or dentures. A copy of the AIMS is located in Appendix 17.3.

The AIMS will be administered at the study site and conducted according to an AIMS administration procedure provided by the sponsor or designee. The AIMS will be administered and scored by the investigator (or designee) using the AIMS scoring descriptors provided by NBI (see Section 8.3.1.1). Subjects will be video recorded according to standardized guidelines for the duration of the AIMS structured examination at screening, Day -1, end of Week 8, and at the follow-up visit (end of Week 52) or early termination. In order to qualify for the study, subjects must have moderate or severe TD at screening as determined by a blinded, external AIMS reviewer based on the AIMS video recording (see inclusion criterion #6 and Section 8.3.1.2). The investigator (or designee) will score AIMS items 1-10 and complete AIMS items 11-12.

The AIMS will be administered at screening, Day -1, during the treatment period (end of Weeks 4, 8, 12, 24, 36, and 48) and at the follow-up visit (end of Week 52) or at early termination. At each timepoint, the AIMS will be administered in the afternoon, between 1200-1700 hours.

8.3.1.1. AIMS Administration and Scoring

During the study, the AIMS will be administered at the study site by the investigator (or designee) according to the AIMS administration procedure. AIMS items 1-10 will be scored and items 11-12 will be completed by the investigator (or designee) administering the AIMS, based on the AIMS scoring descriptors provided by NBI (see Appendix 17.3). If possible, the same person should administer and score the AIMS assessment for an individual subject at all timepoints.

8.3.1.2. AIMS Video Recording and Blinded, External AIMS Reviewer

At screening, Day -1, end of Week 8, and at the follow-up visit (end of Week 52) or early termination, subjects will be video recorded for the duration of the AIMS administration (approximately 10 minutes) according to standardized guidelines provided by the sponsor or designee. Video recordings will be uploaded to a secure, central AIMS server within approximately 24 hours of the AIMS administration. Access to the dedicated central AIMS server will be limited and will require the user to provide a user identification and password to access the secured server and the subject's AIMS video recording. The screening AIMS video recording uploaded to the server will be viewed by the blinded, external AIMS reviewer and the sponsor-designated representatives. The blinded external AIMS reviewer will review the video recordings for the following purposes: (1) determine if the subject has moderate or severe TD at screening (see inclusion criterion #6), and (2) determine if the AIMS was administered according to the AIMS administration procedure and video recorded according to the standardized guidelines (additional timepoints may be reviewed if warranted). In addition, the study center will be asked to submit the original uncompressed AIMS video recording to a core laboratory using an encrypted (password protected) device (eg, flash drive).

8.3.1.3. Blinded, Central AIMS Video Raters

The AIMS video recording files for Day -1, end of Week 8, and at the follow-up visit (end of Week 52) or early termination will be reviewed and scored by blinded, central AIMS video raters. A blinded consensus scoring will be conducted by these raters according to scoring guidelines developed by NBI (see Section 16.3). NBI (or designee) will provide the blinded central AIMS video raters an external hard drive containing subjects' randomized AIMS video recording files to review and score. The central raters will be blinded to the subjects study visits and study drug dose. Two blinded, central raters will together review each AIMS video file from beginning to end and must agree on the score (0 to 4) for AIMS items 1-7. The central AIMS video raters will review and score the AIMS video recordings conducted on Day -1 (baseline), at the end of Week 8, and at the follow-up visit (end of Week 52) or early termination.

8.3.2. Clinical Global Impression – Global Improvement of Tardive Dyskinesia (CGI-TD)

The CGI-TD, 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 TD since the initiation of 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, 1976b).

The investigator or qualified clinician designee (eg, psychologist or social worker) will rate the scale at the scheduled times. If possible, the same person should rate the CGI-TD at all timepoints. The CGI-TD is one of the assessments that will be used by the investigator to determine if a subject is eligible for dose escalation at the end of Week 4. A dose escalation will be allowed at the end of Week 4 if (1) the investigator or designee's assessment of the CGI-TD is "minimally improved", "not changed", "minimally worse", "much worse", or "very much worse", and (2) the safety and tolerability of the current dose is acceptable as determined by a physician.

The CGI-TD will be administered during the treatment period (end of Weeks 4, 8, 12, 24, 36, and 48), and at the follow-up visit (end of Week 52) or at early termination. A copy of the CGI-TD is located in Appendix 17.4.

8.3.3. Patient Global Impression of Change (PGIC)

Subjects will evaluate the change in their TD symptoms since the initiation of study drug dosing choosing one of 7 responses (very much improved, much improved, minimally improved, not changed, minimally worse, much worse, and very much worse). The PGIC will be completed by the subjects during the treatment period (end of Weeks 4, 8, 12, 24, 36, and 48), and at the follow-up visit (end of Week 52) or at early termination A copy of the PGIC is located in Appendix 17.5.

8.3.4. Tardive Dyskinesia Impact Scale (TDIS) and Assessment of Most Bothersome Movement in Tardive Dyskinesia (AMBMTD)

The TDIS and AMBMTD, patient reported outcomes, will be used to assess the impairment and disability associated with dyskinesia and the subject's most bothersome TD movement. The TDIS and AMBMTD will be completed by the subjects at screening, Day -1, during the treatment period (end of Weeks 4, 8, 12, 24, 36, and 48), and at the follow-up visit (end of Week 52) or at early termination. Copies of the TDIS and AMBMTD are provided in Appendix 17.6.

8.4. Pharmacokinetics Evaluations

8.4.1. Blood Sample Collection

Blood samples to determine plasma concentrations of NBI-98854 and its active metabolite NBI-98782 (other metabolites may also be evaluated) will be collected during the treatment period (end of Weeks 4, 8, 12, 24, 36, and 48), and at the follow-up visit (end of Week 52) or at early termination. Samples will be collected in the afternoon between 1200-1700 hours. The exact time of collection will be recorded on the e-CRF.

For each plasma sample, approximately 2 mL of blood will be collected in tubes containing dipotassium ethylenediaminetetraacetic acid (K_2 EDTA). Once obtained, the samples should be thoroughly mixed. If the sample is not centrifuged immediately, the collection tube will be placed upright in a test tube rack and kept on crushed ice. Within 1 hour of collection, samples will be centrifuged at approximately 2,000 g for 10 minutes, preferably under refrigerated conditions (2 to 8°C). The separated plasma will be aspirated using a disposable pipette and then transferred in approximately equal volumes into two vials. The vials will be stoppered and labeled with the study barcode, subject number, primary or back-up sample designation (PK A and PK B, respectively), and nominal study date. The samples will be stored at approximately -20°C within approximately 15 minutes of centrifugation. The date and actual 24-hour clock time of each collection will be recorded on the eCRF. The duplicate plasma sample at each timepoint will be stored and used as backup. These samples (including a manifest with additional information) will be shipped to a central laboratory for analysis preferably on the day of collection to be stored at approximately -70°C. Plasma samples remaining at the end of the study may be used for exploratory assessments.

8.5. Safety Assessments

8.5.1. Safety Assessments for All Subjects

Concomitant medication use and AEs will be monitored throughout the study as described in Sections 8.9.1 and 10, respectively. Additional safety assessments are described in the following sections.

Any abnormal vital sign measurement, clinical laboratory test, or ECG parameter deemed clinically significant by the investigator will be repeated as needed, including test results obtained at the follow-up visit or at early termination, until the value returns to baseline (or within normal limits), or the investigator deems the abnormality to be of no clinical significance. If the investigator determines that a subject has a clinically significant finding of treatment-emergent depression, suicidal ideation, psychiatric symptoms (based upon the C-SSRS, CDSS, MADRS (SIGMA), PANSS, YMRS, or clinical assessment), the finding will be documented as an AE, and appropriate psychiatric evaluation and intervention will provided.

8.5.1.1. Medical History

A general medical history will be obtained at screening and will be updated upon entry into the study on Day -1.

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

8.5.1.2. Physical Examination Including Neurological Assessment, Height, and Weight

A complete physical examination will consist of an assessment of the following: general appearance; skin and mucosa; head, eyes, ears, nose, throat; lymph nodes;

chest/lungs; cardiovascular; abdomen; extremities; musculoskeletal; and neurological system.

A physical examination including weight will be conducted at screening, Day -1, during the treatment period (end of Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48), and at the follow-up visit (end of Week 52) or at early termination. Height will be recorded at screening only. Weight will be recorded with subjects wearing ordinary indoor clothing without shoes. Height and weight will be used to calculate the BMI (kg/m^2).

8.5.1.3. 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 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. Pulse rate will be measured at the wrist for 30 seconds.

Vital sign measurements will be obtained before any scheduled blood sample collection at screening, Day -1, during the treatment period (end of Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48), and at the follow-up visit (end of Week 52) or at early termination.

8.5.1.4. Twelve-lead Electrocardiogram

A standard 12-lead ECG will be conducted in triplicate (1 to 3 minutes apart) after the subject has rested supine for at least 5 minutes. The ECG parameters to be assessed include heart rate, PR interval, QRS duration, QT interval, and QTcF interval (machine readings or calculated). Additionally, the occurrence of de- and re-polarization and rhythm disorders or other abnormalities will be assessed. Based on review of these parameters, the investigator or designee will note if the ECG is Normal, Abnormal not Clinically Significant, or Abnormal Clinically Significant.

The ECGs will be interpreted by the investigator, and if needed, the findings will be confirmed by a cardiologist or internist. Any medically important changes in ECG parameters compared with baseline (Day -1) will be documented on the AE eCRF.

The 12-lead ECG will be conducted at screening, Day -1, during the treatment period (end of Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48), and at the follow-up visit (end of Week 52) or at early termination.

8.5.1.5. Laboratory Assessments

All clinical laboratory tests will be analyzed by a central laboratory, which will provide instructions and supplies to the study staff before study initiation. The laboratory test battery will include routine and screening laboratory tests. Results from samples collected a screening will be reviewed by the investigator or qualified designee on Day -1 to confirm each subject’s eligibility.

The routine laboratory tests (hematology and chemistry) and a urinalysis will be performed under non-fasted conditions at screening, Day -1, during the treatment period (end of Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48), and at the follow-up visit (end of Week 52) or at early termination.

The routine safety laboratory panel will include:

Hematology: complete blood count, including WBC count with differential, red blood count, hemoglobin, hematocrit, platelet count, mean corpuscular hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration, red cell distribution width, and mean platelet volume. A sample for hemoglobin A1c (HbA1c) will also be collected (approximately 4 mL in K_2 EDTA).

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

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

The following additional laboratory tests will be assessed:

Alcohol: An alcohol breathalyzer test will be conducted at screening and Day -1. This test may be randomly performed at any time during the study at the investigator's discretion.

Serology: At screening, samples will be collected from all subjects for HBsAg, HCV-Ab, and HIV-Ab testing. The results of the anti-HIV Ab testing will be retained by the study site under confidential restriction.

UDS: Drug screening for amphetamines, barbiturates, benzodiazepines, phencyclidine, cocaine, opiates, and cannabinoids will be performed at screening and Day -1 and may be randomly performed at any time during the study at the investigator's discretion. In addition, a UDS will be conducted at the study site using a UDS kit provided by the central laboratory and the results will be used to confirm eligibility on Day -1. Subjects with a positive cannabinoid result may be allowed to participate in the study provided that the subject is given thorough counseling and agrees to refrain from using cannabinoids for the duration of his/her study participation. Subjects arriving at the study site clearly intoxicated will not be allowed to participate. Subjects receiving a chronic and stable dose of a benzodiazepine or opioids are allowed into the study (refer to Section 8.9.1).

Prolactin: Blood samples to determine serum prolactin concentration will be collected at Day -1, during the treatment period (end of Weeks 4, 12, 24, 36, and 48), and at the follow-up visit (end of Week 52) or at early termination. Approximately 5 mL of blood will be collected into a serum separator tube (SST).

Pregnancy Test: Pregnancy tests will be performed throughout the study for female subjects who are not postmenopausal for at least 1 year. A serum (β-hCG) pregnancy test will be performed at screening and Day -1. A urine pregnancy test will be performed at Day -1, during the treatment period (end of Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48), and at the follow-up visit (end of Week 52) or at early termination.

For any abnormal tests deemed clinically significant, repeat analysis will be performed until the cause of the abnormality is determined or until the value returns to baseline (or within normal limits), or the investigator deems the abnormality to be of no clinical significance.

The estimated maximum total blood volume collected from each subject during the entire study is shown in Table 3.

Table 3. Estimated Total Blood Sample Volume

Assessment	No of Samples Required	Approximate Volume (mL)	Approximate Total Volume (mL)
Clinical Chemistry	15	5	75
Hematology	15	4	60
HbA1c	15	4	60
Serology	1	10	10
Genotyping	1	4	4
Prolactin	7	5	35
Pharmacokinetics	7	2	14
Biomarkers	7	2	14
Approximate Maximum Total Blood Sample Volume per Subject (mL):			272

HbA1c= hemoglobin A1c.

8.5.1.6. Assessment of Suicidal Ideation and Behavior – Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a validated instrument to prospectively assess suicidal ideation and behavior (http://www.cssrs.columbia.edu). There are versions of the questionnaire designed for use at screening (Baseline/Screening version) and at baseline (Day -1) 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 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 in the 3 months before screening and based on since last visit on Day -1should be excluded (see exclusion criterion #6). A copy of the C-SSRS (Screening/Baseline and Since Last Visit versions) is provided in Appendix 17.7.

The C-SSRS will be administered and scored by the investigator or other qualified site personnel who have completed C-SSRS certification. The C-SSRS will be administered at screening, Day -1, during the treatment period (end of Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48), and at the follow-up visit (end of Week 52) or at early termination. The "Screening/Baseline" version of the scale will be used to evaluate subject eligibility at screening and the 'Since Last Visit' version will be used at all other timepoints.

If at any time after baseline (Day -1) the subject's response to the suicidal ideation section of the C-SSRS is worse than the baseline (Day -1) assessment, it will be documented as an AE. All suicidal behaviors will be documented as an AE. Appropriate psychiatric evaluation and intervention will be provided for any treatment-emergent suicidal behavior or clinically significant suicidal ideation.

8.5.1.7. Evaluation of Akathisia and Extrapyramidal Symptoms - Barnes Akathisia Rating Scale and Simpson-Angus Scale

The 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). A copy of the BARS in included in Appendix 17.8.

The SAS is a validated 10-item scale to evaluate the presence and severity of drug-induced parkinsonism and other extrapyramidal symptoms (Simpson and Angus, 1970). The 10 items focus on clinician-assessed rigidity and each item is rated on a 0 to 4 scale of increasing severity with definitions given for each anchor point. The SAS will also be used as a screening tool; subjects will be excluded if they have a score ≥3 on two or more items at screening or Day -1, excluding Items 8 and 10 (see exclusion criterion #3). A copy of the SAS in included in Appendix 17.9.

The investigator or other qualified site personnel will administer and score the BARS and SAS at Day -1, during the treatment period (end of Weeks 4, 12, 24, 36, and 48), and at the follow-up visit (end of Week 52) or at early termination. The SAS is also administered and scored at screening. If possible, the same person should administer and score these scales at all timepoints.

8.5.2. Safety Assessments in Subjects with Schizophrenia or Schizoaffective Disorder

8.5.2.1. Symptoms of Schizophrenia – Positive and Negative Syndrome Scale (PANSS) for Schizophrenia

The PANSS is a validated clinical instrument used for measuring symptom reduction in patients with schizophrenia (Kay et al., 1987). The scale is divided into three sections with seven items designed to evaluate positive symptoms (symptoms of the disease which manifest as the presence of traits), seven items designed to evaluate negative symptoms (symptoms that manifest as the absence of traits), and 16 items which

address general psychopathology. Each item is scored on a 7-point severity scale (0=absent; 1=minimal; 2=mild; 3=moderate; 4=moderate severe; 5=severe; 6=extreme). The scale also includes three supplementary items that constitute an aggression risk profile; however, these items will not be scored as they are not applicable to the study. Subjects with schizophrenia or schizoaffective disorder must have a PANSS total score of <70 at Day -1 to be eligible for enrollment (see exclusion criterion #22). A copy of the PANSS questions and rating criteria is provided in Appendix 17.10.

The PANSS will be administered and scored by the investigator or other qualified site personnel at Day -1, during the treatment period (end of Weeks 4, 12, 24, 36, and 48), and at the follow-up visit (end of Week 52) or at early termination.

8.5.2.2. Calgary Depression Scale for Schizophrenia (CDSS)

The CDSS is a validated nine-item scale to assess depressive symptoms in patients with schizophrenia (Addington et al., 1990). All nine items are scored on a scale of 0 to 3 (0=absent; 1=mild; 2=moderate; 3=severe) and the CDSS depression total score is obtained by adding each of the item scores. The CDSS will be used to evaluate depressive symptoms throughout the study. The CDSS will also be used as a screening tool; subjects with schizophrenia or schizoaffective disorder must have a score <10 at screening and Day -1 (see exclusion criterion #21). A copy of the CDSS is provided in Appendix 17.11.

The investigator or other qualified site personnel will administer and score the scale at screening, Day -1, during the treatment period (end of Weeks 4, 12, 24, 36, and 48), and at the follow-up visit (end of Week 52) or at early termination. If possible, the same person should administer and score the scale at all timepoints. At each timepoint, the subject will be instructed to provide responses to the CDSS based on feelings and experiences during the 2 weeks prior to the study visit.

8.5.3. Safety Assessments in Subjects with Mood Disorders

8.5.3.1. Young Mania Rating Scale (YMRS)

The YMRS is a validated rating scale to assess manic symptoms over time in patients with mania (Young et al., 1978). The scale consists of 11 items; seven items are scored on a five-point scale (0 to 4) and four items graded on a nine-point scale (0 to 8). Anchor points vary by item, but increasing number value indicates increasing severity of described abnormality for each item. It is possible to score half points between the provided scale points where appropriate. Scoring is based on the subject's report of his or her clinical condition during the past 7 days prior to the study visit as well as clinical observations made during the course of the interview. The YMRS will be used to evaluate mania in subjects with mood disorder throughout the study and will also be used as a screening tool. Subjects must have an YMRS score ≤10 at screening and Day -1 to be eligible for enrollment (see exclusion criterion # 23). A copy of the YMRS is provided in Appendix 17.12.

The investigator or other qualified site personnel will administer and score the scale at screening, Day -1, during the treatment period (end of Weeks 4, 12, 24, 36, and 48),

and at the follow-up visit (end of Week 52) or at early termination. If possible, the same person should administer and score the scale at all timepoints.

8.5.3.2. Montgomery-Asberg Depression Rating Scale (MADRS) using the Structured Interview Guide for the MADRS (SIGMA)

The MADRS is a validated rating scale designed to measure changes in the severity of depressive symptoms (Montgomery and Asberg, 1979). The MADRS consists of 10 items scored on a seven-point scale (0 to 6) with increasing number value indicating increasing severity for each item with anchor points provided at two-point intervals. Scoring is based on a structured clinical interview following the Structured Interview Guide for the MADRS (SIGMA; Williams and Kobak, 2008). Subjects must have a MADRS (SIGMA) score ≤13 at screening and Day -1 to be eligible for enrollment (see exclusion criterion # 27). A copy of the SIGMA is provided in Appendix 17.13.

The investigator or other qualified site personnel will administer and score the scale at screening, Day -1, during the treatment period (end of Weeks 4, 12, 24, 36, and 48), and at the follow-up visit (end of Week 52) or at early termination. If possible, the same person should administer and score the scale at all timepoints. At each timepoint, the subject will be instructed to provide responses based on feelings and experiences during the previous 7 days.

8.6. Exploratory Assessments

8.6.1. Biomarker Analysis

Blood samples will be collected during the study for an exploratory assessment of biomarkers associated with the metabolic profile of NBI-98854. Data collected as part of this exploratory analysis will not be reported as part of the study results.

For each sample, approximately 2 mL of blood will be collected in tubes containing K_2 EDTA. Once obtained, the samples should be thoroughly mixed. If the sample is not centrifuged immediately, the collection tube will be placed upright in a test tube rack and kept on crushed ice. Within 1-hour of collection, samples will be centrifuged at approximately 1,000 g for 10 minutes, preferably under refrigerated conditions (2 to 8°C). The separated plasma will be aspirated using a disposable pipette and then transferred in approximately equal volumes into two vials. The vials will be stoppered and labeled with the study barcode, subject number, primary or backup sample designation (BIO A and BIO B, respectively), and nominal study day. The samples will be stored at approximately -20°C within approximately 15 minutes of centrifugation. These samples will be shipped to a central laboratory to be stored at approximately -70°C.

Blood samples will be collected on Day -1, during the treatment period (end of Weeks 4, 12, 24, 36, and 48), and at the follow-up visit (end of Week 52) or at early termination.

8.7. Specific Study Phase Information

The procedures to be conducted at each study visit are listed in the following sections. Assessments are to be performed for all subjects regardless of underlying disease diagnosis unless otherwise specified. Study visits during the treatment period (end of

Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48), and at the follow-up visit (end of Week 52) or at early termination will have a visit window of ±6 days.

8.7.1. Screening Period (Week -6 to -1)

8.7.1.1. Informed Consent Process

The ICF will be reviewed with subjects. The UBACC will then be administered (Jeste et al., 2007). A copy of the UBACC is provided in Appendix 17.1. 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. Subjects may also be asked to sign an optional release form to allow video recordings of their AIMS assessments to be used for educational purposes. Subjects may refuse to sign the release form with no effect on their study eligibility.

8.7.1.2. Washout of Prohibited Medications

Subjects should discontinue prohibited medications as described in Section 8.9.1 before undergoing screening procedures. Subjects must sign an ICF (subjects must be deemed capable of providing consent using the UBACC as described in Section 8.7.1.1) before any changes in their medication may be made.

8.7.1.3. Screening Procedures

After subjects have signed the ICF (subjects have been deemed to have the capacity to consent to study participation using the UBACC prior to ICF signing), they will undergo screening procedures within 6 weeks prior to enrollment on Day -1. The 6-week screening period begins with the subject's first screening assessment (eg, AIMS, physical examination, vital signs, ECG, clinical laboratory assessments) and not from when the subject signs the ICF, collection of the screening medical history or medications, or pretreatment AEs (unless collected on the same day as the screening assessments). The screening assessments will be performed in the afternoon between 1200-1700 hours.

During the first part of the screening visit, the AIMS (Items 1-12) assessments will be administered and scored by the investigator (or designee). The structured examination will be video recorded (approximately 10 minutes) and uploaded to the central AIMS server within approximately 24 hours. A blinded, external AIMS reviewer will review the video recording to determine study eligibility based on the assessment of global severity of TD (Item 8). In addition, the original uncompressed AIMS video recording files will be sent to a core laboratory using an encrypted (password protected) device.

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

- Inclusion/exclusion criteria.
- Medical history, including medical and psychiatric conditions, demographic information, and alcohol use.
- Physical examination including neurological assessment.

- Height and weight, and perform BMI calculation.
- Vital sign measurements including orthostatic systolic and diastolic blood pressures, orthostatic pulse rate, respiratory rate, and body temperature.
- 12-lead ECG in triplicate.
- A breathalyzer test for alcohol.
- Venous blood sample for clinical laboratory assessments (hematology and clinical chemistry).
- Serology testing (HBsAg, HCV-AB, and HIV-Ab).
- Serum (β-hCG) pregnancy test for female subjects who are not postmenopausal for >1 year.
- Urine sample for urinalysis and UDS.
- Subject to complete the TDIS and AMBMTD.
- Administer C-SSRS (baseline/screening version).
- Administer SAS.
- Administer BPRS.
- Administer CDSS (subjects with schizophrenia or schizoaffective disorder only).
- Administer YMRS and MADRS (SIGMA) (subjects with mood disorders only).
- Record all medications, including over the counter (OTC) medications, herbal remedies, homeopathic preparations, and health and dietary supplements taken by the subject within the previous 30 days and all medications taken for indications of schizophrenia/schizoaffective disorder, mood disorder, EPSE, and TD within the last 2 years (recorded from the time of ICF signing).
- AE monitoring (recorded from the time of ICF signing).

All screening procedures must be completed and results evaluated by the investigator before the baseline procedures are performed on Day -1. The assessment of the global TD symptom severity from the blinded, external AIMS reviewer must be available prior to the Day -1 visit to determine study eligibility.

8.7.2. Baseline (Day -1)

Subjects will return to the study site in the afternoon on Day -1 between 1200-1700 hours. During the first part of the study visit, the AIMS (Items 1-12) will be administered and scored by the investigator (or designee). The structured examination will be video recorded (approximately 10 minutes) and uploaded to the central AIMS server within approximately 24 hours). In addition, the original uncompressed AIMS video recording files will be sent to a core laboratory using an encrypted (password protected) device.

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

- Inclusion/exclusion criteria and medical history update.
- Physical examination, including weight measurement and a neurological assessment.
- Vital sign measurements, including orthostatic systolic and diastolic blood pressures, orthostatic pulse rate, respiratory rate, and body temperature.
- 12-lead ECG in triplicate.
- A breathalyzer test for alcohol.
- Venous blood sample for clinical laboratory tests including routine assessments (hematology and clinical chemistry).
- Venous blood for serum prolactin.
- Venous blood sample for biomarkers.
- Venous blood sample for CYP2D6 genotype status.
- Urine sample for urinalysis and UDS. In addition, the site will need to conduct UDS using the UDS kit provided by the central laboratory to confirm eligibility.
- Urine and serum (β-hCG) pregnancy tests for female subjects who are not postmenopausal for >1 year.
- Subject to complete the TDIS and AMBMTD.
- Administer C-SSRS (since last visit version).
- Administer SAS and BARS.
- Administer CDSS and PANSS (subjects with schizophrenia or schizoaffective disorder only).
- Administer YMRS and MADRS (SIGMA) (subjects with mood disorders only).
- Record prior medications.
- AE monitoring.

The site will access the Interactive Web Response System (IWRS) to obtain an identification number for a kit containing a 4-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 at approximately the same time every day (between 0700-1000 hours). The subjects may take the study drug with or without food and must swallow it with at least 4 oz. of water. A representative from the study site will conduct weekly telephone call to remind the subject take the study medication daily as instructed.
- To record the date and time of each dose on the labels provided on the study drug kit packaging form.
- 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 4 weeks for their next study visit having taken their daily dose of study drug at home.
- To return all used and unused study drug and packaging at the next study visit.

8.7.3. Treatment Period

8.7.3.1. End of Weeks 4, 12, 24, and 36

Subjects will return to the study site in the afternoon between 1200-1700 hours at the end of Weeks 4, 12, 24 and 36. During the first part of the study visit, the following assessments will be performed in the order listed:

- The AIMS (Items 1-12) will be administered and scored by the investigator (or designee).
- The CGI-TD will be assessed by the investigator (or qualified designee). At the end of Week 4, a dose escalation may be allowed based on the CGI-TD assessment and the subject's safety and tolerability of the current dose (refer to Dose Titration Assessment below).

After the AIMS and CGI-TD assessments are conducted, the following study procedures and assessments will be performed:

- Physical examination including weight measurement and a neurological assessment.
- Vital signs, including orthostatic systolic and diastolic blood pressures, orthostatic pulse rate, respiratory rate, and body temperature.
- 12-lead ECG in triplicate.
- Venous blood sample for clinical laboratory assessments (hematology and clinical chemistry).
- Venous blood sample for plasma drug concentration.
- Venous blood sample for serum prolactin.
- Venous blood sample for biomarkers.
- Urine sample for urinalysis.
- Urine sample for pregnancy test (female subjects who are not postmenopausal for >1 year).
- Subject to complete the PGIC, TDIS, and AMBMTD.
- Administer C-SSRS (since last visit version).
- Administer SAS and BARS.
- Administer CDSS and PANSS (subjects with schizophrenia or schizoaffective disorder only).
- Administer YMRS and MADRS (SIGMA) (subjects with mood disorders only).
- AE monitoring.

- Record concomitant medications.
- Study drug accountability.

Dose Titration Assessment

At the end of Week 4, a dose escalation may be allowed if (1) the subject's CGI-TD is "minimally improved", "not changed", "minimally worse", "much worse", or "very much worse" as determined by the investigator or designee, and (2) the safety and tolerability of the current dose is acceptable as determined by a physician. Based these criteria, the investigator will choose one of the following dosing options (also refer to the dose titration algorithm in Section 16.2):

- Dose escalation: The dose of NBI-98854 will be escalated from 40 mg qd to 80 mg qd.
- Maintenance of current dose.

The investigator may decrease the dose to 40 mg at any time after the end of Week 4 (including between scheduled study visits) for any subject who is unable to tolerate the 80 mg dose. These subjects will receive 40 mg for the remainder of the treatment period.

Once a determination of dose escalation, maintenance, or reduction (for subjects who had their dose escalated to 80 mg at the end of Week 4) is made, the IWRS will be accessed to obtain an identification number for a kit containing a 4-week supply of study drug to be dispensed to the subject. The investigator will inform the subject that a dose reduction to 40 mg is allowed if the subject is unable to tolerate the 80 mg dose.

At these visits, subjects will be reminded:

- To take study drug (in the presence of their caregiver, if applicable) each morning at approximately the same time every day (between 0700-1000 hours). The subjects may take the study drug with or without food and must swallow it with at least 4 oz. of water. A representative from the study site will conduct weekly telephone calls to remind the subject take the study medication daily as instructed.
- To record the date and time of each dose on the labels provided on the study drug packaging form.
- 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 4 weeks for their next study visit having taken their daily dose of study drug at home.

8.7.3.2. End of Week 8

Subjects will return to the study site in the afternoon between 1200-1700 hours at the end of Week 8. During the first part of the study visit, the following assessments will be performed in the order listed:

- The AIMS (Items 1-12) will be administered and scored by the investigator (or designee). The structured examination will be video recorded (approximately

10 minutes) and uploaded to the central AIMS server within approximately 24 hours. In addition, the original uncompressed AIMS video recording files will be sent to a core laboratory using an encrypted (password protected) device.

- The CGI-TD will be assessed by the investigator (or qualified designee).

After the AIMS and CGI-TD assessments are conducted, the following study procedures and assessments will be performed:

- Physical examination including weight measurement and a neurological assessment.
- Vital signs, including orthostatic systolic and diastolic blood pressures, orthostatic pulse rate, respiratory rate, and body temperature.
- 12-lead ECG in triplicate.
- Venous blood sample for clinical laboratory assessments (hematology and clinical chemistry).
- Venous blood sample for plasma drug concentration.
- Urine sample for urinalysis.
- Urine sample for pregnancy test (female subjects who are not postmenopausal for >1 year).
- Subject to complete the PGIC, TDIS, and AMBMTD.
- Administer C-SSRS (since last visit version).
- AE monitoring.
- Record concomitant medications.
- Study drug accountability.

The investigator may decrease the dose to 40 mg at any time after the end of Week 4 (including between scheduled study visits) for any subject who is unable to tolerate the 80 mg dose. These subjects will receive 40 mg for the remainder of the treatment period or will be discontinued from the study if they are unable to tolerate the 40 mg dose.

Once a determination of maintenance or reduction is made, the IWRS will be accessed to obtain an identification number for a kit containing a 4-week supply of study drug to be dispensed to the subject.

At this visit, subjects will be instructed:

- To take study drug (in the presence of their caregiver, if applicable) each morning at approximately the same time every day (between 0700-1000 hours). The subjects may take the study drug with or without food and must swallow it with at least 4 oz. of water. A representative from the study site will conduct weekly telephone call to remind the subject take the study medication daily as instructed.
- To record the date and time of each dose on the labels provided on the study drug kit packaging form.
- 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 4 weeks for their next study visit having taken their daily dose of study drug at home.
- To return all used and unused study drug and packaging at the next study visit.

8.7.3.3. End of Weeks 16, 20, 28, 32, 40, and 44

Subjects will return to the study site at any time before 1700 hours at the end of Weeks 16, 20, 28, 32, 40, and 44 and the following assessments will be performed:

- Physical examination including weight measurement and a neurological assessment.
- Vital signs, including orthostatic systolic and diastolic blood pressures, orthostatic pulse rate, respiratory rate, and body temperature.
- 12-lead ECG in triplicate.
- Venous blood sample for clinical laboratory assessments (hematology and clinical chemistry).
- Urine sample for pregnancy test (female subjects who are not postmenopausal for >1 year).
- Urine sample for urinalysis.
- Administer C-SSRS (since last visit version).
- AE monitoring.
- Record concomitant medications.
- Study drug accountability.

The investigator may decrease the dose to 40 mg at any time after the end of Week 4 (including between scheduled study visits) for any subject who is unable to tolerate the 80 mg dose. These subjects will receive 40 mg for the remainder of the treatment period or will be discontinued from the study if they are unable to tolerate the 40 mg dose.

Once a determination of maintenance or reduction is made, the IWRS will be accessed to obtain an identification number for a kit containing a 4-week supply of study drug to be dispensed to the subject.

At these visits, subjects will be reminded:

- To take study drug (in the presence of their caregiver, if applicable) each morning at approximately the same time every day (between 0700-1000 hours). The subjects may take the study drug with or without food and must swallow it with at least 4 oz. of water. A representative from the study site will conduct weekly telephone calls to remind the subject take the study medication daily as instructed.
- To record the date and time of each dose on the labels provided on the study drug packaging form.
- 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 4 weeks for their next study visit having taken their daily dose of study drug at home.
- To return all used and unused study drug and packaging at the next study visit.

8.7.3.4. End of Week 48

Subjects will return to the study site in the afternoon between 1200-1700 hours at the end of Week 48. During the first part of the study visit, the following assessments will be performed in the order listed:

- The AIMS (Items 1-12) will be administered and scored by the investigator (or designee).
- The CGI-TD will be administered by the investigator (or designee).

After the AIMS and CGI-TD assessments are conducted, the following study procedures and assessments will be performed:

- Physical examination including weight measurement and a neurological assessment.
- Vital signs, including orthostatic systolic and diastolic blood pressures, orthostatic pulse rate, respiratory rate, and body temperature.
- 12-lead ECG in triplicate.
- Venous blood sample for clinical laboratory assessments (hematology and clinical chemistry).
- Venous blood sample for plasma drug concentration.

- Venous blood sample for serum prolactin.
- Venous blood sample for biomarkers.
- Urine sample for urinalysis.
- Urine sample for pregnancy test for female subjects who are not postmenopausal for >1 year.
- Subject to complete the PGIC, TDIS, and AMBMTD.
- Administer C-SSRS (since last visit version).
- Administer BARS and SAS.
- Administer CDSS and PANSS (subjects with schizophrenia or schizoaffective disorder only).
- Administer YMRS and MADRS (SIGMA) (subjects with mood disorders only).
- AE monitoring.
- Record concomitant medications.
- Study drug accountability.

The end of Week 48 visit is the end of NBI-98854 treatment period. After all assessments have been completed, subjects will be reminded:

- To contact the study site immediately without waiting for the next study visit to report AEs or before starting any new medication.
- To return approximately 4 weeks for the follow-up visit.

8.7.4. Follow-up Visit - Final Study Visit (End of Week 52 or Early Termination)

Subjects will return to the study site in the afternoon between 1200-1700 hours and the following assessments and procedures will be performed. During the first part of the study visit, the following assessments will be performed in the order listed:

- The AIMS (Items 1-12) will be administered and scored by the investigator (or designee). The structured examination will be video recorded (approximately 10 minutes) and uploaded to the central AIMS server within approximately 24 hours. In addition, the original uncompressed AIMS video recording files will be sent to a core laboratory using an encrypted (password protected) device.
- The CGI-TD will be assessed by the investigator (or qualified designee)

After the AIMS and CGI-TD assessments are conducted, the following study procedures and assessments will be performed:

- Physical examination including weight measurement and a neurological assessment.
- Vital signs, including orthostatic systolic and diastolic blood pressures, orthostatic pulse rate, respiratory rate, and body temperature.
- 12-lead ECG in triplicate.

- Venous blood sample for clinical laboratory assessments (hematology and clinical chemistry).
- Venous blood samples for plasma drug concentration.
- Venous blood sample for serum prolactin.
- Venous blood sample for biomarkers.
- Urine sample for urinalysis.
- Urine sample for pregnancy test for female subjects who are not postmenopausal for >1 year.
- Subject to complete PGIC, TDIS, and AMBMTD.
- Administer C-SSRS (since last visit version).
- Administer BARS and SAS.
- Administer CDSS and PANSS (subjects with schizophrenia or schizoaffective disorder only).
- Administer YMRS and MADRS (SIGMA) (subjects with mood disorders only).
- AE monitoring.
- Record concomitant medications.

After all assessments have been completed, subjects determined to be medically and psychiatrically stable by the investigator will be discharged from the study.

8.8. Study Duration

The expected duration of study participation for each subject is approximately 58 weeks, including up to 6 weeks of screening period, a 48-week NBI-98854 treatment period, and a 4-week follow up period with a follow-up visit approximately 4 weeks after the last dose of study drug.

8.9. Prohibitions and Restrictions

8.9.1. Prior and Concomitant Medication Restrictions

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

Medications to treat psychiatric and medical conditions: All coexistent diseases or conditions will be treated in accordance with prevailing medical practice. All medications to treat the subject's psychiatric and medical conditions should be on a stable treatment regimen (including no changes to the dose and frequency of ongoing medications and no discontinuation of medications) for a minimum of 30 days before

screening procedures. Benzodiazepines must be at a stable dose for 2 weeks before screening. Exceptions may be allowed if discussed with and approved by NBI's medical monitor (or designee) prior to Day -1. If an exception is approved, the subject must be on a stable dose for 30 days prior to Day -1 and the treatment regimens are expected to remain stable during the study. Investigators should document doses of current medication through medical or pharmacy records, confirmation with the subject's caregivers (if applicable), or through reliable subject-reported information (eg, provide a list of medications and doses).

Washout of Prohibited Medications: Subjects should discontinue prohibited medications for at least 30 days before undergoing screening procedures provided they sign an ICF before discontinuation. An exemption may be granted if discussed and approved by NBI's medical monitor (or designee). If an exemption is granted, the subject must complete the 30-day washout prior to Day -1. Discontinuation of the subject's medication should be done under the guidance of the investigator and according to the prescribing information.

Prohibited medications: The following medications are prohibited from 30 days prior to screening until the follow-up visit (end of Week 52 or early termination):

- **Antiemetics**: Metoclopramide, prochlorperazine, and promethazine are prohibited.
- **Antihypertensives**: Reserpine (known to irreversibly bind to VMAT2) is prohibited.
- **Botulinum toxin:** Botulinum toxin injections are prohibited starting 90 days prior to screening and during the study.
- **CYP3A4 inducers:** Strong inducers of CYP3A4 (eg, phenobarbital, rifabutin, rifampin, primidone, phenytoin, St. John's Wort) are prohibited. The use of carbamazepine is permitted if approved by NBI's medical monitor (or designee) prior to Day -1.
- **Dopamine agonists and precursors:** Dopamine receptor agonists (eg, ropinirole) and precursors (eg, carbidopa/levodopa) are prohibited.
- **Monoamine Oxidase Inhibitors (MAOIs):** All MAOIs (eg, isocarboxazid, phenelzine, selegiline, tranylcypromine) are prohibited.
- **Stimulants**: Stimulants (eg, amphetamine, methylphenidate, ephedrine, pseudoephedrine, phenylephrine, and phenylpropanolamine) are prohibited.
- **VMAT2 Inhibitors**: VMAT2 inhibitor medications (eg, tetrabenazine, reserpine) are prohibited, except for NBI-98854.
- **Drugs known to increase the QT interval:** The use of medication known to increase the QT interval may be allowed if approved by the Sponsor. QTcF must be ≤450 msec for males or ≤470 msec for females at screening and baseline.

  Some of the medications that may increase the QT interval include the following:

  - Antipsychotics: chlorpromazine, thioridazine and ziprasidone
  - Antidepressants: citalopram
  - Antibiotics: azithromycin, clarithromycin, erythromycin, moxifloxacin
  - Antiarrhythmics: quinidine, procainamide, amiodarone, sotalol

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

Allowed as needed use: As needed use of over-the-counter and prescription medications is allowed to treat headaches, pain, respiratory symptoms, acute allergic symptoms, and allergies.

Medications recommended for insomnia include eszopiclone 7.5 mg, zaleplon 10 mg, zolpidem 5 mg for female subjects and 10 mg for male subjects, or Silenor 3 or 6 mg at night as needed.

8.9.2. General and Dietary Restrictions

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

- Return to the study site at baseline (Day -1), for visits during the NBI-98854 treatment period (end of Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48) and at the follow-up visit (end of Week 52) or at early termination.
- Not to use any prohibited concomitant medication (Refer to Section 8.9.1).
- Subjects must limit alcohol use to less than 7 drinks per week during the course of the study.
- Not to donate blood during the study, including the screening period, and for 4 weeks after completion of the study.
- Not to participate in an investigational drug study for at least 30 days after the last dose of study drug or 30 days after study completion, whichever is longer.

8.10. Withdrawal Criteria

8.10.1. Reasons for Withdrawal

Subjects are free to discontinue their participation in the study at any time and without prejudice to further treatment. The investigator must withdraw any subject from the study who requests to be withdrawn.

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

- If the type, frequency, or severity of any AE become unacceptable/intolerable.
- If the subject is unable to tolerate the starting dose or resumption of the previous dose.
- QTcF value >500 msec or subject has a clinically significant ECG change.
- 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.
- Does not follow guidelines specified in the protocol.

- Is lost to follow-up.
- Does not continue to meet entry criteria.
- Subject is confirmed to be pregnant.

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

- ALT or AST ≥2.5 times ULN or GGT ≥3.0 times ULN or total bilirubin value exceeds 2.0 times ULN or serum creatinine value exceeds 1.5 times ULN.
- Requires a medication that is prohibited by the protocol (refer to Section 8.9.1).
- Is non-compliant with the dosing regimen (<80% dosing compliance) as verified by drug accountability (Refer to Section 9.6).

8.10.2. Handling of Withdrawals

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

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

8.10.3. Sponsor's Termination of Study

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

9. STUDY DRUG

9.1. Study Drug Supplies

Neurocrine Biosciences, Inc. or its designee will provide the clinical site with a supply of study drug sufficient for the completion of the treatment period of the study together with the respective certificates of analysis.

Neurocrine Biosciences, Inc. or its designee will provide study drug as NBI-98854 40 mg capsules. The NBI-98854 40 mg capsule is a white, opaque, HPMC No. 3 size capsule containing 40 mg of NBI-98854 (dose is of the free base) and is formulated using [redacted] shells.

9.2. Study Drug Storage

NBI-98854 capsules must be stored at controlled room temperature (20˚C to 25˚C or 68˚F to 77˚F) under the conditions specified in the Investigator's Brochure and in a locked area accessible only to the pharmacist (or designee) until dispensing.

Excursions outside this range will be allowed provided they meet the following conditions:

- Storage between refrigerated conditions (2˚C or 36˚F) and CRT (25˚C or 77˚F) for an unspecified length of time.
- Storage at temperatures above 25˚C (77˚F) but no more than 30˚C (86˚F) for up to 3 months.
- Storage at temperatures above 30˚C (86˚F) but no more than 40˚C (104˚F) for up to 24 hours.

9.3. Study Drug Packaging and Labeling

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

Study drug will be supplied as capsules in child-resistant blistercard dispensers; each blistercard contains enough study drugs for 28 days of dosing plus 6 extra dose days. The blistercards will contain capsules of NBI-98854 40 mg.

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

9.4. Blinding

This study is an open label study.

9.5. Study Drug Administration

Subjects will self-administer study drug (in the presence of their caregiver, if applicable) in the morning at approximately the same time (between 0700-1000 hours). Subjects may take the study drug with or without food and must swallow it with at least 4 oz. of water every day during the 48-week treatment period. 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 1800 hours. The subject will need to skip the dose for that day if he or she is unable to take the study drug before 1800 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.

9.6. Drug Compliance and Accountability

Subjects will bring all unused study drug and empty drug packaging material to the study site at each study visit for drug accountability and reconciliation by study site personnel. A compliance check will be performed by counting the capsules returned at each study visit. A representative from the study site will call the subjects weekly to remind them to take their study medication daily.

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

9.7. 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 the designee. The investigator must provide a written explanation for any destroyed or missing study drug or study drug materials.

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

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

10. ADVERSE EVENTS

All AEs, whether observed by the investigator, reported by the subject, noted from laboratory findings, or identified by other means, will be recorded from the time the subject signed the ICF until the subject's final study visit (end of Week 52 or early termination).

10.1. Definition

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. During the study, clinically significant adverse changes in clinical status, ECGs, laboratory values (not associated with an AE or concurrent medical condition), or physical examinations are considered AEs. Any subject complaint associated with such an abnormal finding will also be reported as an AE.

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

If at any time after the baseline visit (Day -1) 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.
- Recurrence of TD symptoms, unless worsened from baseline.
- Pregnancy.

10.1.1. Intensity of Adverse Events

Adverse events must be graded for intensity. An intensity category of mild, moderate, or severe, as defined in Table 4, must be entered on the AE eCRF. It should be noted that the term "severe" used to grade intensity is not synonymous with the term "serious."

Table 4. Intensity of Adverse Events

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

10.1.2. 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 adverse event. (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.

10.2. Recording Adverse Events

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

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

- Serious adverse event, including death (refer to Section 10.4).
- Pregnancy (Refer to Section 10.5).
- Events of 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.

10.3. Post Study Follow-Up of Adverse Events

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

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

10.4. Serious Adverse Events

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

10.4.1. Definition of a Serious Adverse Event

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

- Death.
- A life-threatening adverse event. 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.

10.4.2. Managing Serious Adverse Events

Subjects experiencing an SAE or an emergency situation will be examined by a physician as soon as possible. The physician in attendance will do whatever is medically needed for the safety and well-being of the subject. The subject will remain under observation as long as medically indicated. Appropriate laboratory tests 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 Medical Monitor (and the IRB, if necessary) immediately (within 24 hours) of the SAE and the outcome of the SAE.

If within the time of informed consent until 30 days after the last dose of study drug (or final study visit, whichever is longer in duration) an investigator becomes aware of an SAE, then the event must be documented and reported as described in Section 10.4.3.

10.4.3. Reporting Serious Adverse Events and Other Immediately Reportable Events

Serious AEs and other immediately reportable events (as defined in Section 10.2) must be reported within 24 hours of first knowledge of the event by study personnel to the NBI Medical Monitor or NBI Clinical Drug Safety (CDS) Department. Reports of SAEs or pregnancies should be followed by an email or fax of the SAE or Pregnancy Form. It is important that the investigator provide his or her assessment of relationship to study drug at the time of the initial SAE report.

For SAEs or Other Immediately Reportable Events, contact CDS:

CDS telephone:
CDS facsimile:
CDS e-mail:
NBI Medical Monitor: **Telephone**
Cell phone

10.4.4. Expedited Safety Reports

Neurocrine Biosciences, Inc. or its representatives will submit an Expedited Safety Report for any suspected adverse reaction (as defined in Section 10.1.2) that is considered both serious and unexpected within 15 calendar days and for any unexpected fatal or life-threatening experience within 7 calendar days via telephone or facsimile; or according to country-specific regulations.

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

10.5. 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 NBI-98854 will be followed to assess for congenital anomaly. Subjects must be counseled at all visits to continue using two forms of nonhormonal contraception or hormonal contraception (see inclusion criterion #2 in Section 7.1) until the end of the follow-up visit (end of Week 52). 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 stop taking the study medication and return to the study site within 24 hours and undergo a serum pregnancy test to confirm pregnancy.

All confirmed pregnancies, in subjects who received study drug, must be immediately reported to NBI (Refer to Section 10.4.3 for contact information), and followed by email or fax of the pregnancy form to NBI CDS. A first trimester ultrasound will be required for all confirmed pregnancies. Pregnancies in subjects who received NBI-98854 will be followed until resolution (ie, termination [voluntary or spontaneous] or birth).

11. DOCUMENTATION OF DATA

11.1. Case Report Form

The CRF data for this study are being collected with an electronic data capture (EDC) system ( ) provided by . 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, , while the validation of the study-specific eCRFs will be conducted by NBI and the required documentation will be maintained in the Trial Master File.

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

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

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

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

11.2. Data Capture, Review, and Validation

Data entered in the EDC system will be verified against the source data by NBI (or designee). Any discrepancies will be corrected on-line by an authorized site personnel. After completion of the entry process, automated (computer-generated) logic checks will run in order to identify items such as inconsistent study dates. In addition, manual review/checks may be performed by NBI on the data. Any

inconsistencies/errors/omissions identified will be sent to the study site (via an electronic query) for the necessary corrections to be made to the eCRF. Once entered and saved in an eCRF, data immediately become part of the study database and are available to NBI.

11.3. Coding Dictionaries

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

12. STATISTICAL AND ANALYTICAL PLAN

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

12.1. Analysis Sets

The safety analysis set will be the primary analysis set used for the summary of data for this study. This analysis set will include all subjects who are dispensed study drug. Additional analysis sets may be specified in the expanded Statistical Analysis Plan (SAP).

12.2. Sample Size

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

12.3. Handling of Missing Data

Conventions for the handling of missing data will be described in the SAP.

12.4. Enrollment and Disposition of Subjects

The summary of subject enrollment and disposition will display the number of subjects who received at least one dose of study drug, who completed the NBI-98854 treatment period, and who completed the study. The number of subjects who did not complete the study will be summarized also, both overall and according to the reason for early discontinuation. A separate summary of enrollment by study center will also be provided.

12.5. Demographics Data and Baseline Characteristics

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

Medical history will be summarized in frequency tables (number and percentage of subjects) by MedDRA system organ class (SOC) and preferred term.

12.6. Study Drug Dosing

The estimated number of doses of study drug taken during the 4-week intervals between consecutive scheduled visits during the treatment period will be summarized with descriptive statistics by visit. The cumulative estimated number of doses taken through Week 48 will be summarized also. Additionally, the number of subjects at each dose level (40 mg or 80 mg) will be summarized by visit along with the number of subjects who have a dose reduction.

12.7. Pharmacokinetic Data

The plasma concentrations of NBI-98854 and its active metabolite NBI-98782 (and other metabolites that may be evaluated) will be summarized with descriptive statistics by timepoint (Week 4, 8, 12, 24, 36, 48, and 52) and the most recent NBI-98854 dose (40 mg or 80 mg) received prior to that timepoint. These summaries will also be generated separately for CYP2D6 poor metabolizers vs. non poor metabolizers. Concentrations below the lower limit of quantification will be set equal to zero for all plasma concentration summaries.

12.8. Efficacy Data

The efficacy measures in this study include the AIMS as scored by the blinded central AIMS video raters, CGI-TD, PGIC, TDIS, and AMBMTD. The AIMS as scored by the investigators will be evaluated as an exploratory measure. Descriptive statistics will be provided for various derived variables based on the efficacy measures at each measurement timepoint, both overall and by underlying disease category. The efficacy variable of primary interest is the AIMS dyskinesia total score, which is calculated as the sum of items 1 through 7. Descriptive statistics will be presented for the AIMS dyskinesia total score at each visit and for the changes from baseline (Day -1) at each visit after Day -1. In addition, the percentage of AIMS responders (subjects with a 50% or greater reduction from baseline in the AIMS dyskinesia total score) will be summarized.

12.9. Safety Data

Treatment-emergent AEs (TEAEs), categorized by SOC and preferred term as defined by the MedDRA coding dictionary (Version 12.0), will be summarized overall and by NBI-98854 dose (with assignment to dose based on the last dose received prior to the AE onset). Adverse events reported during the NBI-98854 treatment period and the posttreatment period will be summarized separately. These TEAE tables will include the number of events, number of unique subjects experiencing each event, and percentage of subjects experiencing each event.

Adverse events will be also be tabulated in terms of the number and percentage of subjects experiencing events by maximum intensity, and additional summaries will be presented which include only TEAEs that are considered to be possibly or definitely related to study drug.

Separate summaries will be generated for AEs leading to premature discontinuation from the study, SAEs, and deaths.

Clinical laboratory tests (hematology and clinical chemistry), vital signs, ECG, physical examination, PANSS, CDSS, C-SSRS, BARS, SAS, YMRS, and MADRS (SIGMA) data at each study visit will be summarized overall and by NBI-98854 dose with descriptive statistics. Prior and concomitant medications will be summarized also.

12.10. Interim Analyses

One or more interim data locks and analyses will be performed during the study for interim data review.

12.11. Software

Statistical calculations and summaries will be generated using

13. REGULATORY AND ETHICAL ISSUES

13.1. General Legal References

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

13.2. Institutional Review Board

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

13.3. 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 will be notified of all amendments to the protocol. Amendments to the protocol will not be implemented until written IRB approval has been received.

13.4. Required Documents

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

- Signed copy (original) of the approved protocol.
- Completed and signed statement of investigator (Form FDA 1572 and/or Clinical Trial Site Form – as applicable)

- Curriculum vitae and current medical license of the investigator and subinvestigators.
- Financial disclosure information as required.
- Letter of approval from the IRB for both protocol and consent form.
- Copy of the IRB-approved written ICF to be used.
- Laboratory documents (certifications/accreditations, normal ranges) if not provided by a central laboratory.

13.5. Informed Consent

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

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

13.6. Study Monitoring

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

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

13.7. Quality Assurance

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

13.8. Record Retention

Federal regulations require that records of drug disposition, CRFs, and all reports of this investigation shall be retained by the investigator for a minimum of 2 years after notification by NBI that the regulatory authorities have been notified of the study's termination, or 2 years after approval of the marketing application. If the investigator is unable to retain the study documents for the required amount of time, NBI must be informed of the individual who will be assuming this responsibility.

13.9. Confidentiality

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

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

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

14. STUDY COMMENCEMENT AND DISCONTINUATION

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

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

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16. SUPPLEMENTS

16.1. Neuroleptic-Induced Tardive Dyskinesia Diagnostic Criteria

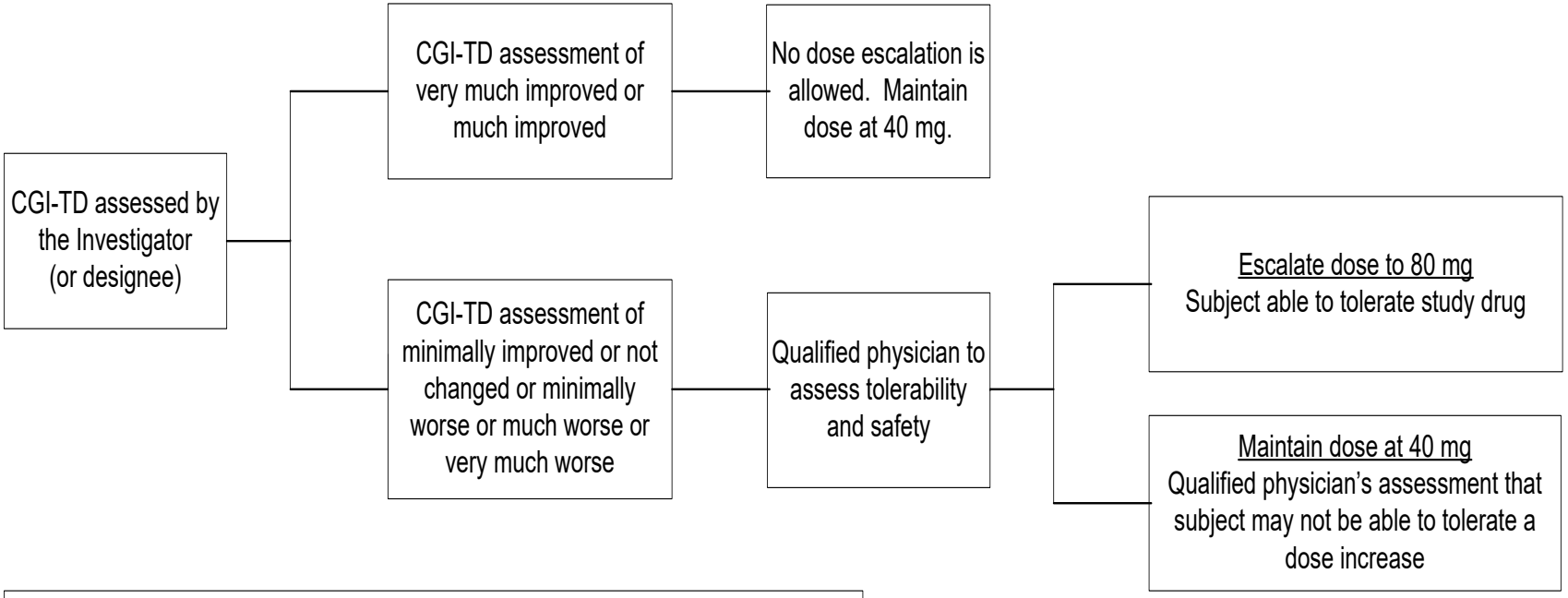
The DSM-IV provides following diagnostic criteria for neuroleptic-induced tardive dyskinesia (refer to DSM-IV 333.82):

- A person who has taken neuroleptics for at least 3 months* develops at least two movements of at least mild intensity while taking a neuroleptic.
- A person who has taken neuroleptics for at least 3 months* develops at least one movement of at least moderate intensity while taking a neuroleptic.
- A person who has taken neuroleptics for at least 3 months* develops at least two movements of at least mild intensity within 4 weeks of the discontinuation of the neuroleptic.
- A person who has taken neuroleptics for at least 3 months* develops at least one movement of at least moderate intensity within 4 weeks of the discontinuation of the neuroleptic.

*1 month if older than 60 years

16.2. NBI-98854-1402 Dose Titration Algorithm

End of Week 4



At any time after the end of Week 4

Resumption to 40 mg dose for subjects who are unable to tolerate the dose escalation to 80 mg dose. Subjects will remain at this dose for the remainder of the treatment period.

Discontinuation from the study

Subject who are unable to tolerate the starting dose (40 mg) or resumption of the 40 mg dose will be discontinued from the study.

16.3. Blinded Central AIMS Video Raters' Consensus Scoring Process

1. The blinded central AIMS video raters must be neurologists who are movement disorder experts.
2. Each blinded central AIMS video rater will be assigned a unique rater ID number.
3. The blinded central AIMS raters must complete practice review and consensus scoring of AIMS videos provided by the sponsor (using AIMS video files from subjects who are not participating in the current study) prior to scoring any study subjects' AIMS videos.
4. Each AIMS video file to be scored will be assigned a randomization number thereby blinding the central AIMS video raters to the subject's study visits and dose.
5. A face-to-face meeting will be set up for two blinded central AIMS video raters to meet at a mutual location. The sponsor (or designee) will provide the following materials at the meeting for the raters to review and score the AIMS video files:
   - HD TV
   - Laptop computer
   - External Hard Drive containing study subjects' randomized AIMS video files.
   - AIMS paper Case Report Form (CRF).
6. At the meeting, two blinded central AIMS video raters will together review each video file from beginning to end. If required, the raters can review each video multiple times but must not re-review the video file after scores have been generated.
7. The two blinded, central AIMS video raters will score AIMS Items 1-7. Both must agree (have consensus) on a score (0 to 4) based on the following AIMS descriptors.

Score	Descriptors
0	No dyskinesia
1	Minimal or Slight dyskinesia: Low amplitude, present during some but not most of the exam
2	Mild dyskinesia: Low amplitude and present during most of exam (or moderate amplitude and present during some of exam)
3	Moderate dyskinesia: Moderate amplitude and present during most of exam
4	Severe dyskinesia: Maximal amplitude and present during most of exam

8. One of the blinded central AIMS video raters will enter the item scores on a paper CRF for each AIMS video file reviewed. Both raters will complete the rater ID number, and sign and date each paper CRF in the space provided.
9. The completed paper CRF will be collected by the sponsor to enter the AIMS scores into the study database.

17. APPENDICES