

# CLINICAL STUDY PROTOCOL

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## **A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of NBI-98854 in Adult Subjects with Tourette Syndrome**

Study No.: NBI-98854-1505

Development Phase: Phase 2

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*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 Practices (GCP) (Harmonized)
- United States (US) Code of Federal Regulations (CFR); US Food and Drug Administration (FDA)

**CLINICAL STUDY TITLE:**

A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of NBI-98854 in Adult Subjects with Tourette Syndrome

**PROTOCOL No.:** NBI-98854-1505

**As Agreed:**

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Principal Investigator Signature

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Date

**PRINCIPAL INVESTIGATOR:**

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(Print Principal Investigator Name)

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## 2. SYNOPSIS

**Title of Study:**

A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of NBI-98854 in Adult Subjects with Tourette Syndrome

**Study centers:**

Approximately 40 study centers in the United States.

**Objectives:**

- To evaluate the efficacy of 2 active doses of NBI-98854 (40 mg and 80 mg) administered once daily in adult subjects with Tourette syndrome (TS).
- To assess the safety and tolerability of repeated daily doses of NBI-98854 in adult subjects with TS.
- To evaluate plasma exposure of NBI-98854 and its metabolite, NBI-98782, following repeated daily doses of NBI-98854.

**Study Design:**

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel group study in a total of 90 male and female subjects, 18 to 64 years of age, with a Diagnostic and Statistical Manual of Mental Disorders, 4th or 5th Editions (DSM-IV or -V) diagnosis of TS.

After providing informed consent, subjects will be screened to determine eligibility within 21 days (Days -21 to -1) before the start of study drug dosing on Day 1. On Day -1 (baseline), eligible subjects will return to the study center for collection of baseline safety and efficacy assessments and collection of a blood sample for subsequent determination of their cytochrome P450 2D6 (CYP2D6) metabolizer status. Subjects who continue to be eligible for the study will then be randomized (1:1:1) to placebo or 1 of 2 active doses of NBI-98854 (40 mg or 80 mg). Study drug will be administered in a double-dummy fashion throughout the 8-week double-blind treatment period. Beginning on Day 1, study drug will be administered at home once daily in the morning with a standard breakfast through Week 8. The NBI-98854 80 mg dose will be titrated in a blinded fashion (subjects will receive 40 mg for the first week followed by 80 mg for the remainder of the 8-week treatment period).

At any time, if the subject is unable to tolerate their current dose, the investigator may decrease the subject's dose. The investigator is allowed to reduce the subject's dose only one time during the study. Subjects who have had a dose reduction and are unable to tolerate their new dose will be discontinued from the study. To maintain the study blind, subjects receiving 40 mg or placebo who have a dose reduction will continue to receive their current dose and subjects receiving 80 mg will be reduced to 40 mg.

During the double-blind treatment period, subjects will return to the study center at 2-week intervals (end of Weeks 2, 4, 6, and 8) for study assessments and dispensing of study drug (Weeks 2, 4, and 6 only). All subjects who have completed the 8-week treatment period will enter a 2-week follow-up period with a follow-up visit at Week 10 (or early termination).

Efficacy, safety, and study drug exposure will be assessed at scheduled times throughout the study.

**Study Population:**

Approximately 90 male and female adult subjects between 18 and 64 years of age, with a DSM-IV or -V diagnosis of TS will be enrolled into this study. The subjects must have at least moderate current TS symptomatology, as defined by a Clinical Global Impression of Tics (CGI-Tics)–Severity score of  $\geq 4$  (ie, moderately ill) and a Yale Global Tic Severity Scale (YGTSS), Total Tic Severity Score of at least 20 points at screening. In addition, subjects with Tourette spectrum diagnoses (eg, obsessive-compulsive disorder [OCD], Attention-Deficit Hyperactivity Disorder [ADHD], etc) must have a stable psychiatric status.

**Duration of treatment and study participation:**

The expected duration of study participation for each subject is approximately 13 weeks, including up to 21 days of screening, an 8-week double-blind treatment period, and a 2-week drug-free follow-up period.

**Investigational product, dose, and mode of administration:**

NBI-98854 will be supplied as capsules containing 40 mg of NBI-98854 (free base). The NBI-98854 capsules will be taken with a standard breakfast.

NBI-98854 will be administered in a double-dummy fashion. Subjects randomized to receive NBI-98854 40 mg will receive one 40 mg capsule and one matching placebo capsule. Subjects randomized to receive NBI-98854 80 mg will receive two 40 mg capsules (except during the first 7 days prior to dose titration when subjects will receive a 40 mg dose as one 40 mg capsule and one matching placebo capsule).

**Reference therapy, dose, and mode of administration**

Matching placebo capsules are identical in appearance and will be orally administered in a double-blind, double-dummy manner according to randomization on an identical schedule to those receiving NBI-98854. The placebo capsules will be taken with a standard breakfast.

Placebo will be administered in a double-dummy fashion. Subjects randomized to placebo will receive two matching placebo capsules.

**Criteria for evaluation:****Efficacy:**

The following efficacy assessments will be administered at screening, baseline (Day -1), Weeks 2, 4, 6, and 8, and at the follow-up visit (Week 10 or early termination):

- Yale Global Tic Severity Scale (YGTSS; primary assessment)
- Rush Video-based Tic Rating Scale (RTRS)
- Premonitory Urge for Tics Scale (PUTS)
- Clinical Global Impression of Change-Tourette Syndrome (CGI-TS)-Improvement
- Clinical Global Impression of Tics (CGI-Tics)-Severity

The CGI-Tics-Severity scale will be used to rate the Investigator's assessment of the severity of tic symptoms at screening and baseline. Both the CGI-Tics-Severity and CGI-TS-Improvement scales will be assessed by the investigator at Weeks 2, 4, 6, and 8; and at the follow-up visit (Week 10 or early termination).

**Safety:**

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

- Adverse events
- Clinical laboratory tests (hematology, clinical chemistry, and urinalysis)
- Serum prolactin
- Vital signs (including orthostatic blood pressures and pulse)
- Physical examinations
- 12-lead electrocardiograms
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Extrapyramidal Symptom Rating Scale-Abbreviated (ESRS-A)
- Structured Interview Guide for the Hamilton Depression Rating Scale, 17-Item (SIGH-D-17)
- Yale-Brown Obsessive-Compulsive Scale (Y-BOCS)

**Pharmacokinetics**

Blood samples to evaluate plasma concentrations of NBI-98854, and the metabolite NBI-98782 will be collected during the treatment period (end of Weeks 2, 4, 6, and 8) and at the follow-up visit (Week 10 or at early termination).

**Statistical methods:**

The primary efficacy endpoint is the change from baseline (Day -1) to Week 8 in the YGTSS Total Tic Score (TTS). Secondary efficacy endpoints include the YGTSS Global Tic Severity score mean change from baseline to Week 8, the RTRS total score mean change from baseline to Week 8; the PUTS total score mean change from baseline to Week 8, the CGI-TS-Improvement mean score change from baseline to Week 8, and the CGI-Tics-Severity score mean change from baseline to Week 8.

Statistical comparisons between each NBI-98854 treatment group and placebo will be performed for the efficacy endpoints. The primary analysis of the TTS change from baseline will be a mixed-effect model repeated measures (MMRM) analysis including the scores at Weeks 2, 4, 6, and 8 based on the per-protocol and intent-to-treat analysis sets. Similar methods of analysis will be used for the secondary efficacy endpoints.

Safety and plasma drug and metabolite concentration data will be summarized by treatment and timepoint using descriptive statistics.

### 3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADHD	Attention-Deficit Hyperactivity Disorder
AE	Adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	Alanine transaminase
AST	Aspartate transaminase
β-hCG	β-human chorionic gonadotropin
CBIT	Comprehensive Behavioral Intervention for Tics
CDS	Clinical Drug Safety
CFR	Code of Federal Regulations
CGI-TS	Clinical Global Impression of Change-Tourette Syndrome
CGI-Tics	Clinical Global Impression of Tics
C <sub>max</sub>	Maximum plasma concentration
CRT	Controlled room temperature
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	Cytochrome P450
DSM-IV or -V	Diagnostic and Statistical Manual of Mental Disorders 4 <sup>th</sup> or 5 <sup>th</sup> Editions
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EDTA K <sub>2</sub>	Dipotassium ethylenediaminetetraacetic acid
ESRS-A	Extrapyramidal Symptom Rating Scale-Abbreviated
FDA	[United States] Food and Drug Administration
GCP	Good Clinical Practices
GGT	Gamma-glutamyl transferase
HBsAg	Hepatitis B surface antigen
HCV-Ab	Hepatitis C virus antibody
HIV-Ab	Human immunodeficiency virus antibody
ICF	Informed consent form
IRB	Institutional Review Board
ITT	Intent-to-treat

IWRS	Interactive Web Response System
MAOI	Monoamine oxidase inhibitor
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effects model repeated measures
NBI	Neurocrine Biosciences, Inc.
NOAEL	No observed adverse effect level
PK	Pharmacokinetic(s)
PP	Per-protocol
PUTS	Premonitory Urge for Tics Scale
QTcF	Corrected QT interval using Fridericia's formula
RTRS	Rush Video-based Tic Rating Scale
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SIGH-D-17	Structured Interview Guide for the Hamilton Depression Rating Scale, 17-Item
TD	Tardive dyskinesia
TEAE	Treatment-emergent adverse event
TS	Tourette syndrome
TTS	Total Tic Score
ULN	Upper limit of normal
US	United States
VMAT2	Vesicular monoamine transporter 2
WBC	White blood cell
Y-BOCS	Yale-Brown Obsessive-Compulsive Scale
YGTSS	Yale Global Tic Severity Scale

## 4. ETHICS

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

- Good Clinical Practice: Consolidated Guideline (International Conference on Harmonization 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 50, 54, 56, 312, and 314).

The ethical requirements of Institutional Review Boards/Ethics Committees (IRBs/ECs) and the Informed Consent Forms (ICFs) are discussed in [Section 14](#).

## 5. INTRODUCTION

### 5.1. Background

Tourette Syndrome (TS) is a movement disorder characterized by the presence of chronic motor and one or more vocal tics that often appear in childhood or early adolescence ([APA DSM-IV, 1994](#); [APA DSM-V, 2013](#)). Tics are defined as rapid, non-rhythmic, stereotyped motor movements or vocalizations, and are typically categorized as simple or complex based on their overt features. Simple tics are brief, meaningless actions (eg, forceful blinking of the eyes or grunting) and complex tics are slower, more purposeful behaviors (eg, gyrating or uttering phrases; [Leckman et al., 1989](#); [Cavanna and Nani, 2013](#); [Shprecher and Kurlan, 2009](#)). The tics follow a waxing and waning course over time, and must be recurrent for a period of more than 1 year to qualify for diagnosis. In addition to tic phenomena, TS may also present with a constellation of symptoms that are part of a broader “TS spectrum,” which can include obsessive-compulsive behaviors, attention-deficit/hyperactivity disorder, and impulsive or antisocial behavior ([Chen et al., 2012](#); [Felling and Singer, 2011](#)).

It has been well established that TS is predominantly a disorder of childhood with a mean or median age of onset of approximately 6 years of age ([Leckman et al., 1998](#); [Robertson, 2011](#); [Jankovic and Kurlan, 2011](#); [Swain et al., 2007](#)). Tic symptomatology usually becomes the most severe around age 10 and by the time adulthood is achieved at 18 years of age, the majority of patients are either tic-free or their symptoms have significantly improved ([Leckman et al., 1998](#); [Kurlan, 2010](#)). TS symptoms may also occur in adults and these tic phenomena appear to be a re-emergence or an exacerbation of childhood onset TS ([Chouinard and Ford, 2000](#); [Jankovic and Kurlan, 2011](#)).

Persistent tics can have a significant impact on patient quality of life and often lead to impaired psychosocial functioning. Some of these problems include social isolation, bullying, physical discomfort (with pain or injury), and poor academic and/or work performance ([Roessner et al., 2013](#)). Psychosocial stressors can, in turn, exacerbate tic symptomatology. It is under these conditions that pharmacological interventions are often considered ([Chen et al., 2012](#); [Shprecher & Kurlan, 2009](#); [Roessner et al., 2013](#)).

Neuropathological models have been proposed to explain the symptomatic features of TS, and converging lines of empirical evidence consistently implicate dopaminergic dysfunction and dysregulation within prefrontal cortex-basal ganglia circuitry (Felling and Singer, 2011; Pourfar et al., 2011). Functional neuroimaging studies have identified a pattern of prefrontal cortex hypermetabolism and reduced striatal activity in TS patients (Baxter and Guze, 1993; Braun et al., 1993; Pourfar et al., 2011). Pharmacotherapeutic approaches aimed at blocking postsynaptic dopamine-2 receptors (eg, haloperidol and pimozide) have demonstrated efficacy in reducing TS symptoms. In this regard, modulation of dopaminergic tone through the administration of a Vesicular monoamine transporter 2 (VMAT2) inhibitor, like NBI-98854, may also be an effective treatment option for tic suppression.

Currently the only approved agent with VMAT2 inhibitory activity is tetrabenazine, a dopamine-depleting agent recently approved for the treatment of chorea associated with Huntington's disease. Use of tetrabenazine for the treatment of 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 depletion, 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.

## **5.2. NBI-98854**

NBI-98854 is an orally active valine ester of a VMAT2 inhibitor (NBI-98782) and is currently under development at NBI for the treatment of neuroleptic-induced Tardive dyskinesia (TD), TS, and other involuntary movement disorders. Metabolism of NBI-98854 is characterized by conversion of NBI-98854 to NBI-98782, and cytochrome P450 (CYP) 3A4/5 dependent mono-oxidation to NBI-136110. All three entities, namely, NBI-98854, NBI-98782 and NBI-136110, have the ability to bind to and inhibit VMAT2. However, NBI-98782 is the most potent and appears to be responsible for the majority of the observed pharmacological activity of VMAT2 inhibition.

The intravenous and oral NBI-98854 pharmacokinetics (PK) has been studied in mice, rats, monkeys, dogs, and humans. In animals, orally administered NBI-98854 is rapidly absorbed and relatively slowly converted to NBI-98782, such that animals are exposed to both NBI-98854 and NBI-98782. Dose-dependent increases in exposure to both NBI-98854 and NBI-98782 were seen in animal studies. NBI-98854 appears to cause little or no CYP enzyme inhibition or induction at pharmacologically relevant concentrations. 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; 8 Phase 1 studies in healthy subjects and subjects with hepatic impairment, and 4 Phase 2 studies in subjects with TD and a clinical diagnosis of schizophrenia or schizoaffective disorder, mood disorder, or gastrointestinal disorder. The Phase 1 studies have evaluated the PK of NBI-98854 administered as an oral solution or capsule formulation, PK 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 being reached within 1 hour. The metabolite NBI-98782 was formed gradually with maximum plasma concentration being reached 4 to 10 hours postdose. 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 or CYP2D6 inhibitors is expected to increase the maximum plasma concentration ( $C_{max}$ ) 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 was given to subjects with moderate or severe hepatic impairment.

Results from Phase 2 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). 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 50 mg NBI-98854 daily dosing and also in subjects originally assigned to placebo who went on to receive 50 mg NBI-98854 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 AIMS dyskinesia total score in the NBI-98854 group compared to placebo. A statistically significant higher responder rate (ie,  $\geq 50\%$  improvement in AIMS dyskinesia total score from baseline) was also observed in the NBI-98854 group compared with placebo.

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 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.

### **5.3. Study and Dose Rationale**

The present study is a Phase 2, randomized, double-blind, placebo-controlled, parallel fixed-dose study to evaluate the efficacy, safety and tolerability of 2 doses of NBI-98854 (40 mg and 80 mg) for the treatment of TS. Medically stable adult subjects with a diagnosis of DSM-IV or -V of TS will be randomized in a 1:1:1 ratio to self-administer placebo, NBI-98854 40 mg, or NBI-98854 80 mg (approximately n=30 per treatment group) once daily for 8 weeks. Subjects will be required to have at least moderate TS as determined by the Yale Global Tic Severity Scale (YGTSS) and the CGI-Tics-Severity scale.

Clinical data from subjects with the hyperkinetic movement disorder, TD, who were administered doses of 12.5 mg to 100 mg per day in Phase 2 trials indicate that NBI-98854 is generally well tolerated and associated with dose-related efficacy in this disorder. Exposure-response modeling of the Phase 2 data in TD patients indicates that a steady state  $C_{max}$  of 20 to 40 ng/mL NBI-98782 is an appropriate plasma concentration range for pharmacodynamic response. Following consultation with the FDA Division of Psychiatry Products, the 40 mg and 80 mg doses of NBI-98854 were selected for evaluation in the Phase 3 TD program. It is anticipated that these same doses in the current study of adult TS subjects will provide the same exposure levels of NBI-98854 previously observed in the clinic, and will be associated with acceptable tolerability and robust efficacy, and will also allow for the drug to be administered regardless of CYP2D6 genotype or concomitant medication status. In the TD patient population, doses below 40 mg are well tolerated but below the minimal effective dose, and doses above 80 mg afforded minor incremental benefit, but at an increased risk of adverse events (AEs).

## 6. STUDY OBJECTIVES

The objectives of this clinical study are as follows:

- To evaluate the efficacy of 2 active doses of NBI-98854 (40 mg and 80 mg) administered once daily in adult subjects with TS.
- To assess the safety and tolerability of repeated daily doses of NBI-98854 in adult subjects with TS.
- To evaluate plasma exposure of NBI-98854 and its metabolite, NBI-98782, following repeated daily doses of NBI-98854.

## 7. OVERVIEW OF STUDY DESIGN

### 7.1. Study Design

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel group study in a total of 90 male and female subjects, 18 to 64 years of age, with a Diagnostic and Statistical Manual of Mental Disorders, 4th or 5th Editions (DSM-IV or V) diagnosis of TS.

After providing informed consent, subjects will be screened to determine eligibility within 21 days (Days -21 to -1) before the start of study drug dosing on Day 1. Subjects may also be asked to sign an optional release form to allow their Rush Video-based Tic Rating Scale (RTRS) video recordings to be used for educational purposes.

On Day -1 (baseline), eligible subjects will return to the study center for collection of baseline safety and efficacy assessments and collection of a blood sample for subsequent determination of their cytochrome P450 2D6 (CYP2D6) metabolizer status. Subjects who continue to be eligible for the study will then be randomized (1:1:1) to placebo or 1 of 2 active doses of NBI-98854 (40 mg or 80 mg). A 2-week supply of study drug will be dispensed. Study drug will be administered in a double-dummy fashion throughout the 8-week double-blind treatment period. Beginning on Day 1, study drug will be administered at home once daily in the morning with a standard breakfast through Week 8. The NBI-98854 80 mg dose will be titrated in a blinded fashion (subjects will receive 40 mg for the first week followed by 80 mg).

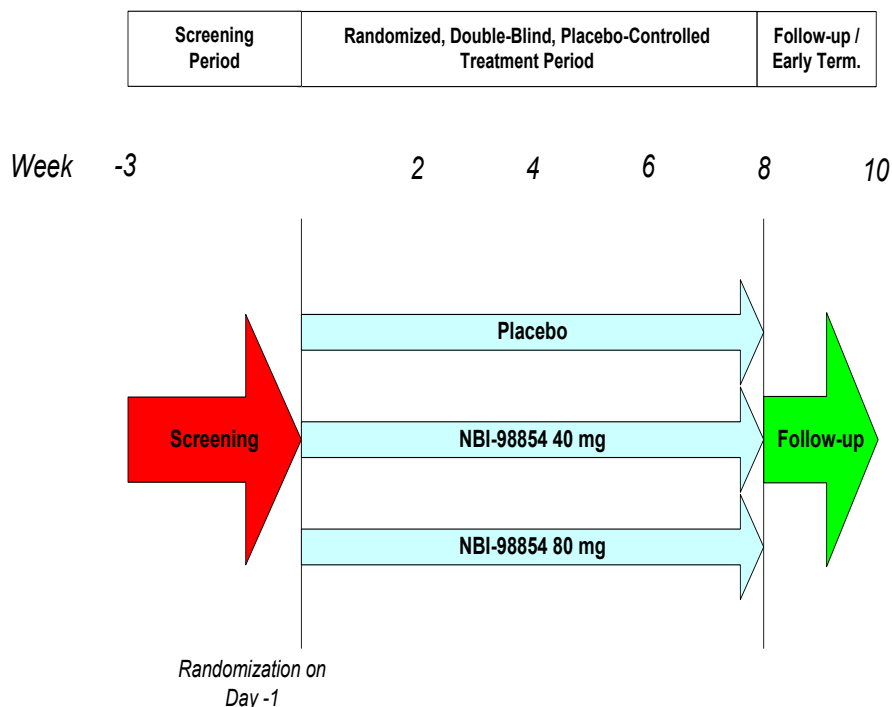
At any time, if the subject is unable to tolerate their current dose, the investigator may decrease the subject's dose. The investigator is allowed to reduce the subject's dose only one time during the study. Subjects who have had a dose reduction and are unable to tolerate the new dose will be discontinued from the study. To maintain the study blind, subjects receiving 40 mg or placebo who have a dose reduction will continue to receive their current dose and subjects receiving 80 mg will be reduced to 40 mg.

During the double-blind treatment period, subjects will return to the study center at 2-week intervals (end of Weeks 2, 4, 6, and 8) for study assessments and dispensing of study drug (Weeks 2, 4, and 6 only). All subjects who have completed the 8-week treatment period will enter a 2-week follow-up period with a follow-up visit at Week 10 (or early termination).

Efficacy assessments for TS symptomatology will be performed using the YGTSS (primary), the RTRS, the Premonitory Urge for Tics Scale (PUTS), the Clinical Global Impression of

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

**Figure 1: Study Design Schematic**



## **8. STUDY POPULATION**

This study will be conducted in approximately 90 male and female adult subjects with a DSM-IV or -V diagnosis of TS. Subjects must meet all of the inclusion criteria and none of the exclusion criteria to enter the study.

### **8.1. Inclusion Criteria**

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

1. Have documentation of written informed consent.
2. Be male or female, aged 18 to 64 years, inclusive.
3. Be in good general health, as determined by medical history, physical examination, clinical laboratory assessments, and 12-lead ECG.
4. Have a DSM-IV or -V diagnosis of TS.
5. Have at least moderate current tic severity, as defined by a CGI-Tics-Severity score of  $\geq 4$  (ie, moderately ill) and a YGTSS Total Tic Score (TTS) of  $\geq 20$  at screening. This determination must be independently confirmed by the blinded external video reviewer using a video recording of the subject's YGTSS assessment administered at the clinical site by the investigator (or designee).
6. Have TS symptoms that impair school, occupational, and/or social function.
7. Subjects with TS spectrum diagnoses (eg, obsessive-compulsive disorder [OCD], Attention-Deficit Hyperactivity Disorder [ADHD]) must have a stable psychiatric status as clinically determined by the investigator at screening and baseline.
8. If medications are being used to treat TS symptoms and/or TS spectrum diagnoses, subjects must be on stable doses of these medications for a minimum of 30 days before baseline (Day -1), and the medication regimen is expected to remain stable throughout the study period. The use of dopamine antagonists (eg, pimozide, haloperidol, aripiprazole, risperidone, clozapine, olanzapine, ziprasidone) and/or tetrabenazine to treat TS symptoms is prohibited. Other non-dopaminergic tic suppression therapy (eg, clonidine, guanfacine) is allowed during the study period as long as the dose regimen has been stable for a minimum of 30 days before baseline (Day -1).
9. Subjects with stable medical conditions requiring medications that are not prohibited per protocol must be on stable doses of these medications for a minimum of 30 days before baseline (Day -1), and the medication regimen is expected to remain stable throughout the study period.
10. Subjects of childbearing potential who do not practice total abstinence must be instructed on the proper use of barrier methods of contraception and agree to use hormonal contraception or two forms of nonhormonal contraception (dual contraception) consistently from screening until 30 days after the last dose of study drug.

Acceptable methods of contraception include the following:

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

The following subjects are not required to use contraception:

- Subjects who practice total abstinence from sexual intercourse as the preferred lifestyle are not required to use contraception (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.
11. Female subjects of childbearing potential must have a negative serum  $\beta$ -human chorionic gonadotropin ( $\beta$ -hCG) pregnancy test at screening and negative urine pregnancy test at baseline (Day -1).
  12. Have a body mass index (BMI) of 18 to 40 kg/m<sup>2</sup> (inclusive) at screening. (BMI is defined as the subject's weight in kg divided by the square of the subject's height in meters.)
  13. Subjects must have a negative urine drug screen (negative for amphetamines, barbiturates, benzodiazepine, phencyclidine, cocaine, opiates, or cannabinoids) at screening and baseline (Day -1). Subjects who are on stable doses of prescribed and supervised (not prn) benzodiazepines, opiates, or psychostimulants (for subjects with comorbid ADHD) are allowed to participate in the study. Subjects with a positive urine drug screen for cannabinoids are eligible for participation if the use is for medicinal purposes and there is no indication of cannabinoid abuse.
  14. Subjects must have a negative alcohol breath test at screening and baseline (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).
  16. Be willing and able to adhere to the study regimen and study procedures described in the protocol and informed consent forms, including all requirements at the study center and return for the final study day.

## **8.2. Exclusion Criteria**

Subjects will be excluded from the study if they:

1. Have an unstable medical condition or chronic disease (including history of neurological, hepatic, renal, cardiovascular, gastrointestinal, pulmonary, or endocrine disease), or malignancy that could confound interpretation of study outcome.

2. Had a medically significant illness within 30 days of screening.
3. Excessive use of tobacco and/or nicotine-containing products (based on the investigator's assessment) within 30 days of screening.
4. Have a history of substance (drug) dependence or abuse within the 3 months before baseline (Day -1), as defined in the DSM-IV (Substance Dependence or Abuse) or DSM-V (Substance Use Disorder).
5. Are currently pregnant or lactating.
6. Have a known history of neuroleptic malignant syndrome.
7. Have a known history of long QT syndrome or cardiac arrhythmia.
8. Have a screening or Day -1 average triplicate ECG QT interval corrected for heart rate using corrected QT interval using Fridericia's formula (QTcF) of >450 msec (males) or >470 msec (females) or the presence of any clinically significant cardiac abnormality.
9. Have any of the following laboratory test abnormalities at screening:
  - Serum creatinine >1.5 times the upper limit of normal (ULN).
  - Aspartate transaminase (AST)  $\geq 2.5$  times ULN.
  - Alanine transaminase (ALT)  $\geq 2.5$  times ULN.
  - Gamma-glutamyl transferase (GGT)  $\geq 3.0$  times ULN.
  - Total bilirubin >1.5 mg/dL.
10. Have any of the following hematologic abnormalities at screening:
  - Hemoglobin <10.0 g/dL.
  - White blood cell (WBC) count <3.0 x 10<sup>3</sup>/mm<sup>3</sup>.
  - Platelet count <100,000/mm<sup>3</sup>.
11. Have a hematologic malignancy or solid tumor diagnosed within 3 years prior to screening, with the exception of localized skin cancer or carcinoma in situ of the cervix.
12. Have biochemistry or hematology not within the laboratory's reference range and deemed by the investigator to be clinically significant at screening.
13. Have a positive human immunodeficiency virus antibody (HIV-Ab) test result, hepatitis B surface antigen (HBsAg) test result or hepatitis C virus antibody (HCV-Ab) test result at screening.
14. Have received an investigational drug within 30 days before screening or plan to use an investigational drug (other than NBI-98854) during the study.
15. Receive any excluded concomitant medication (refer to [Section 9.8.1](#)).
16. Have initiated Comprehensive Behavioral Intervention for Tics (CBIT) during the screening period or at baseline (Day -1) or plan to initiate CBIT during the study.
17. Have a blood loss  $\geq 550$  mL or donated blood within 30 days before baseline (Day -1).

18. 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) within the past year before screening based on the Columbia Suicide Severity Rating Scale (C-SSRS) should be excluded.
19. Have ingested foods containing poppy seeds within 7 days before screening and baseline (Day -1).
20. Have an allergy, hypersensitivity, or intolerance to tetrabenazine.
21. Have a history of or suspected poor compliance in clinical research studies.

### **8.3. Subject Identification and Replacement**

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

### **8.4. Randomization**

An Interactive Web Response System (IWRS) will be used to randomize subjects to 1 of 3 double-blind treatment assignments during the 8-week double-blind treatment period: placebo or 1 of 2 active NBI-98854 doses (NBI-98854 40 mg or 80 mg) in a 1:1:1 ratio. Randomization will occur at baseline (Day -1) after the subject is confirmed to have met the eligibility criteria. Treatment assignments will be made according to a computer-generated randomization schedule. Investigators or a designee will access the IWRS to obtain randomization assignments.

## **9. STUDY EVALUATIONS**

### **9.1. Schedule of Assessments**

A schedule of assessments that summarizes the frequency and timing of all assessments is provided in [Table 1](#). No protocol related procedures should be performed before subjects provide written informed consent. Subject related events and activities including specific instructions, procedures, concomitant medications, dispensing of study drug, and descriptions of AEs should be recorded in the appropriate source documents and eCRFs.

**Table 1: Schedule of Assessments**

Procedure	Screening Period	Baseline	Double-Blind Placebo-Controlled Treatment Period				Follow-up/ Early Term. <sup>a</sup>
	Week -3 to -1 Visit 1	Day -1 2	2 <sup>b</sup> 3	4 <sup>b</sup> 4	6 <sup>b</sup> 5	8 <sup>b</sup> 6	10 <sup>b</sup> 7
Informed consent	X						
Inclusion/exclusion criteria	X	UPDATE					
Medical history	X	UPDATE					
Physical examination (including weight)	X	X	X	X	X	X	X
Height	X						
Vital signs	X	X	X	X	X	X	X
12-lead ECG <sup>c</sup>	X	X	X	X	X	X	X
Pregnancy test <sup>d</sup>	X (s)	X (u)	X (u)	X (u)	X (u)	X (u)	X (u)
Serology (HBsAg, HCV-Ab and HIV-Ab)	X						
Clinical laboratory tests <sup>e</sup>	X	X	X	X	X	X	X
Urine drug screen <sup>f</sup>	X	X					
Alcohol breath test	X	X					
Genotype blood sample		X					
Serum prolactin		X	X	X	X	X	X
Plasma sample for NBI-98854 and metabolite concentrations			X	X	X	X	X
YGTS (including video recording)	X	X	X	X	X	X	X
RTRS	X	X	X	X	X	X	X
PUTS	X	X	X	X	X	X	X
CGI-Tics – Severity	X	X	X	X	X	X	X
CGI-TS-Improvement			X	X	X	X	X
C-SSRS	X	X	X	X	X	X	X
ESRS-A		X	X	X	X	X	X
Y-BOCS and SIGH-D-17	X	X	X	X	X	X	X
Randomization		X					
Study drug dosing at home <sup>g</sup>			X	X	X	X	
Dispense study drug <sup>h</sup>		X	X	X	X		
Study drug accountability <sup>i</sup>			X	X	X	X	
AE monitoring	X	X	X	X	X	X	X
Prior and concomitant medications	X	X	X	X	X	X	X
Outpatient clinic visits	X	X	X	X	X	X	X

AE=adverse event; CGI-Tics=Clinical Global Impression of Tics; CGI-TS=Clinical Global Impression of Change-Tourette Syndrome; C-SSRS=Columbia Suicide Severity Rating Scale; Y-BOCS=Yale-Brown Obsessive-Compulsive Scale; ECG=Electrocardiogram; ESRS-A=Extrapyramidal Symptom Rating Scale-Abbreviated; ET=early termination; SIGH-D-17=Structured Interview Guide for the Hamilton Depression Rating Scale ; HBsAg=hepatitis B surface antigen; HCV-Ab=hepatitis C virus antibody; HIV-Ab=human immunodeficiency virus antibody; PUTS=Premonitory Urge for Tics Scale; RTRS=Rush Video-Based Tic Rating Scale; S=serum; U=urine; YGTS=Yale Global Tic Severity Scale.

- Final study visit for subjects who complete the study (or early termination).
- Visit window of  $\pm 3$  days.
- 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 that will be assessed include HR, QTc, QTcF, and PR intervals, and QRS duration based on the ECG machine readings (QTcF may be calculated).
- A serum pregnancy test will be conducted at screening, and urine pregnancy tests will be conducted at all other study visits for female subjects of childbearing potential.
- Clinical laboratory tests include hematology, chemistry, and urinalysis. All blood samples will be obtained under non-fasted conditions.
- Urine drug screen will be analyzed by the central laboratory. In addition, urine testing kits will be provided by the central laboratory to confirm negative drug screen on Day -1. A urine drug screen using a kit provided by the central laboratory may be conducted at the clinical site at any time during the study if the subject is suspected of substance or drug abuse.



g. Study drug will be taken once daily at home starting on Day 1 (in the morning at approximately the same time) throughout the double-blind treatment period.

Footnotes continue on the next page.

- h. Study drug will be dispensed on Day -1 and at Weeks 2, 4, and 6. The NBI-98854 80 mg dose will be titrated in a blinded fashion (subjects will receive 40 mg for the first week followed by 80 mg). Subjects will record the date and time study drug was taken as indicated in the study drug kit.
- i. At Weeks 2, 4, 6, and 8 subjects will return all empty study drug packaging and unused study drug, and a compliance check will be performed by counting the capsules returned at each study visit.

## **9.2. Screening and Baseline Assessments**

### **9.2.1. Genotyping**

On Day -1 (baseline), a blood sample will be collected from enrolled subjects for the analysis of CYP2D6 status (ie, extensive, intermediate, poor, or ultrarapid metabolizers). Approximately 4 mL of blood will be collected in tubes containing dipotassium ethylenediaminetetraacetic acid (EDTA K<sub>2</sub>). After the sample is obtained, it should be thoroughly mixed. The vials will be stoppered and labeled with the study barcode and subject number. The samples will be stored at approximately -20°C within approximately 15 minutes of collection. The collection and submission of medical information will be accomplished with strict adherence to professional standards of confidentiality. Genotyping blood samples collected from subjects will be shipped to a central laboratory for analysis.

## **9.3. Efficacy Assessments**

### **9.3.1. Yale Global Tic Severity Scale**

The YGTSS will serve as the primary assessment of tic behaviors associated with TS ([Leckman et al., 1989](#)). The YGTSS is designed to rate the overall severity of motor and phonic tic symptoms across a range of dimensions: number, frequency, intensity, complexity, and interference. The scale also includes an impairment assessment. The YGTSS will be administered by the investigator (or qualified designee) using a computer-based structured clinical interview. At each timepoint, the YGTSS interview will be video recorded in its entirety. The video recording will follow a standardized set of guidelines and the recorded video will be uploaded to a secure central server. A blinded, external video reviewer will access the central server to view the recording and (1) confirm the subject's TS severity as at least moderate (at screening only), and (2) determine if the YGTSS interview program was administered properly. The computer software system for the YGTSS administration, Rater Station™ (Bracket Global LLC, Philadelphia, PA), will prompt the investigator (or a qualified designee), a trained and certified rater, to enter a score for each item of the scale based on subject responses during the structured clinical interview. The software will also generate individual scores for each item of the scale (tandem rating) and will generate the TTS and the Global Tic Severity Score.

The YGTSS will be administered at screening, baseline (Day -1), during the double-blind treatment period (Weeks 2, 4, 6, and 8), and at the follow-up visit (Week 10 or early termination). A copy of the YGTSS is provided in [Appendix 17.1](#).

### **9.3.2. Rush Video-Based Tic Rating Scale**

A modified RTRS will be used in this study that includes short video recordings to measure 5 tic variables: number of body areas affected, frequency of motor and phonic tics, and severity of motor and phonic tics (Goetz et al., 1999). Subjects must be video recorded while seated comfortably in a quiet room facing the camera with their hands in their lap and feet on the floor. If desired, subjects may read a book, as long as these activities do not block the camera's view of their face, neck and shoulders, arms, and legs. Subjects should be video recorded for a total of approximately 10 minutes. The investigator (or designee) should be present for approximately the first 2.5 minutes to aid the subject in adjusting to the procedure. The subject should then be video recorded alone for approximately 5 minutes. The investigator (or designee) should then re-enter the room and remain seated quietly in a corner of the room for approximately the last 2.5 minutes of the video recording. The RTRS videos will be reviewed and scored by a blinded central rater using a triple-blind scoring process.

The RTRS will be administered at screening, baseline (Day -1), during the double-blind treatment period (Weeks 2, 4, 6, and 8), and at the follow-up visit (Week 10 or early termination). A copy of the modified RTRS is provided in [Appendix 17.2](#).

### **9.3.3. Premonitory Urge for Tics Scale**

The Premonitory Urge for Tics Scale (PUTS) is a valid and reliable instrument for quantifying the premonitory urge phenomena associated with tics (Woods et al., 2005). Each of the 9 items in the PUTS is rated on a 4-point scale (1 = not at all true, 2 = a little true, 3 = pretty much true, 4 = very much true) and summed to yield a total score reflecting the presence and frequency of pre-tic (ie, premonitory) urges along with relief that may be experienced after tics have been completed.

The investigator (or designee) will administer the PUTS at screening, baseline (Day -1), during the double-blind treatment period (Weeks 2, 4, 6, and 8), and at the follow-up visit (Week 10 or early termination). A copy of the PUTS is provided in [Appendix 17.3](#).

### **9.3.4. Clinical Global Impression of Tourette Syndrome**

The CGI-Tics – Severity and CGI-TS – Improvement scales will be used to rate the subject's overall severity and overall improvement of TS.

The CGI-Tics-Severity scale will be used to assess overall severity on a 7-point scale (range; 1=normal, not at all ill to 7=among the most extremely ill patients). The CGI-Tics – Severity will be assessed by the investigator at screening, baseline (Day -1), Weeks 2, 4, 6, and 8 and at the follow-up visit (Week 10 or upon early termination). A copy of the CGI-Tics – Severity scale is provided in [Appendix 17.4](#).

The CGI-TS – Improvement scale will be used to assess overall improvement since the initiation of study drug dosing on a 7-point scale (range; 1=very much improved to 7=very much worse). CGI-TS-Improvement scales will be assessed by the investigator at Weeks 2, 4, 6, and 8 and at the follow-up visit (Week 10 or upon early termination). A copy of the CGI-TS-Improvement scale is provided in [Appendix 17.5](#).

## 9.4. Pharmacokinetic Evaluations

Blood samples to evaluate plasma concentrations of NBI-98854 and the metabolite NBI-98782 will be collected during the treatment period (end of Weeks 2, 4, 6, and 8) and the follow-up visit (Week 10 or early termination). The exact time of collection will be recorded on the eCRF.

For each plasma sample, approximately 2 mL of blood will be collected in tubes containing EDTA K<sub>2</sub>. 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 to be stored at approximately -70°C. Plasma samples remaining at the end of the study may be used for exploratory assessments.

## 9.5. Safety Assessments

Concomitant medication use and AEs will be monitored throughout the study as described in Sections [Section 9.8.1](#) and [Section 11](#), respectively. Additional safety assessments are described in the following sections.

Any abnormal vital sign measurement, physical examination finding, clinical laboratory test, or ECG parameter deemed clinically significant by the investigator will be repeated, including test results obtained on the follow-up visit (Week 10) 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, SIGH-D-17, Y-BOCS, or clinical assessment), the finding will be documented as an AE, and appropriate psychiatric evaluation and intervention will be provided.

### 9.5.1. Vital Sign Measurements

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

Vital sign measurements will be collected at screening, Day -1, and Weeks 2, 4, 6, 8, and 10 (or upon early termination).

### **9.5.2. Medical History**

A medical history will be taken at the screening visit and updated on Day -1. The age at TS diagnosis will be documented for all subjects; if necessary, subject age at TS onset can be estimated by the investigator based upon available clinical information.

### **9.5.3. Physical Examination, Including Height and Weight**

The complete physical examination will consist of an assessment of general appearance, skin and mucosae, head, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest/lungs, cardiovascular, abdomen, extremities, musculoskeletal, and neurological system. A complete physical examination including weight will be performed at screening, Day -1, and Weeks 2, 4, 6, 8, and 10 (or upon early termination). Height will be measured at screening only. Height and weight will be measured with subjects not wearing shoes.

### **9.5.4. Electrocardiogram**

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

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

### **9.5.5. Clinical Laboratory Assessments**

All clinical laboratory assessments will be performed by a central laboratory, which will provide instructions and supplies to the study staff before study initiation. The instructions will be included in a laboratory manual. The laboratory test battery will include routine and screening laboratory tests. Laboratory samples will be collected in the following approximate amounts: 4 mL for hematology and 5 mL for serum chemistry (includes screening serum pregnancy tests for female subjects of childbearing potential).

Clinical safety laboratory assessments will be performed at screening, Day -1 (baseline), and Weeks 2, 4, 6, 8, and 10 (or upon early termination). There are no fasting requirements for laboratory assessments.

The following clinical safety laboratory assays will be performed:

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

Clinical Chemistry: sodium, potassium, calcium, magnesium, chloride, blood urea nitrogen, bicarbonate, creatinine, uric acid, albumin, alkaline phosphatase, lactate dehydrogenase, ALT,

AST, GGT, creatine kinase, total bilirubin, total cholesterol, triglycerides, total protein and glucose.

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

The following additional laboratory tests will be performed:

Serum Prolactin: Blood samples to determine serum prolactin concentration will be collected at baseline (Day -1), at Weeks 2, 4, 6, and 8; and at the follow-up visit (Week 10 or upon early termination). Approximately 5 mL of blood will be collected into a serum separator tube. Serum prolactin samples will be shipped to a central laboratory for analysis.

Serology: Blood will be collected for HIV-Ab, HBsAg, and Hepatitis C virus antibody (HCV-Ab) testing at screening (as part of clinical chemistry). The results of the Anti-HIV-Ab testing will be retained by the study site under confidential restriction. The following approximate amounts will be collected: 10 mL.

Urine Drug Screen and Alcohol Breathalyzer Test: The urine drug screen will test for amphetamines barbiturates, phencyclidine, benzodiazepines, cannabinoids, cocaine, and opiates. Urine testing kits will be provided by the central laboratory to confirm negative drug screen prior to dosing. A separate urine sample will also be sent to the central laboratory for analysis. A urine drug screen and alcohol breathalyzer test will be performed at screening and on Day -1. Subjects with a positive urine drug screen for cannabinoids are eligible for participation if the use is for medicinal purposes and there is no indication of cannabinoid abuse. A urine drug screen using a kit provided by the central laboratory may be conducted at the clinical site at any time during the study if the subject is suspected of substance or drug abuse.

Pregnancy Tests: A pregnancy test will be conducted for female subjects of childbearing potential. A serum pregnancy test will be conducted at screening and a urine pregnancy test will be conducted on Day -1, Weeks 2, 4, 6, and 8, and at the follow-up visit (Week 10 or upon early termination).

#### **9.5.6. Columbia-Suicide Severity Rating Scale**

The C-SSRS is a validated instrument to prospectively assess suicidal ideation and behavior (<http://www.cssrs.columbia.edu>). There are versions of the questionnaire designed for use at screening (Baseline/Screening version) and at baseline and visits throughout the study (Since Last Visit version). All versions of the C-SSRS include a series of screening questions related to suicidal ideation and suicidal behavior. Subject responses of 'yes' to one or more screening questions will prompt additional questions that evaluate frequency and intensity of suicidal ideation and/or behavior. Subjects with any lifetime suicidal behavior or suicidal ideation of type 4 (active suicidal ideation with some intent to act, without specific plan) or type 5 (active suicidal ideation with specific plan and intent) in the 1 year before screening based on the C-SSRS should be excluded (see [exclusion criterion #17 in Section 8.2](#)).

The C-SSRS will be administered and scored by the investigator or qualified study center personnel at screening, Day -1, and Weeks 2, 4, 6, 8, and 10 (or upon early termination). Copies of each of the C-SSRS versions are provided in [Appendix 17.6](#) and [Appendix 17.7](#).

### 9.5.7. Extrapyramidal Symptom Rating Scale-Abbreviated

The ESRS-A is a psychometrically validated instrument that assesses 4 types of movement disorders: parkinsonism, akathisia, dystonia, and tardive dyskinesia (TD) (Chouinard and Margolese, 2005). The investigator (or designee) will administer the ESRS-A at baseline (Day -1), during the treatment period (Weeks 2, 4, 6, and 8), and at the follow-up visit (Week 10 or upon early termination). A copy of the ESRS-A is provided in [Appendix 17.10](#). Yale-Brown Obsessive Compulsive Scale

The Y-BOCS is a semistructured interview designed to rate the severity of obsessive and compulsive symptoms. The investigator (or designee) will administer the Y-BOCS at screening, Day -1, and Weeks 2, 4, 6, 8, and 10 (or upon early termination). A copy of the Y-BOCS is provided in [Appendix 17.8](#).

### 9.5.8. Structured Interview Guide for the Hamilton Depression Rating Scale

The Hamilton Depression Rating Scale is one of the most commonly used scales for rating depression. To standardize the administration of this scale, the Investigator (or designee) will use the SIGH-D-17. This clinician-rated interview consists of 17 items. Each item on the questionnaire is scored on a 3, 4, or 5-point scale and individual item scores are summed up to yield a total score. The investigator (or designee) will administer the SIGH-D-17 at screening, Day -1, and Weeks 2, 4, 6, 8, and 10 (or upon early termination). A copy of the SIGH-D-17 is provided in [Appendix 17.9](#).

### 9.5.9. Estimated Total Blood Sample Volume Required by Study

The estimated total blood sample volume for each subject is presented in Table 2. These estimates include samples to be collected during screening, the treatment periods, and at the follow-up visit (or early termination).

**Table 2: Estimated Total Blood Sample Volume**

Parameter	Number of Samples Required	Approximate Volume (mL)	Approximate Total Volume (mL)
Serum chemistry <sup>a</sup>	7	5	35
Hematology	7	4	28
Genotyping	1	4	4
Serology	1	10	10
Serum prolactin	6	5	30
Pharmacokinetics	5	2.5 <sup>b</sup>	12.5
Approximate Maximum Total Blood Sample Volume per Subject (mL):			<b>119.5</b>

a Includes pregnancy test for female subjects who are of childbearing potential at screening.

b Includes 0.5 mL of discard volume per sample.

## **9.6. Specific Study Information**

After providing subject informed consent subjects will undergo screening procedures within 21 days of Day -1. Subjects may also be asked to sign an optional release form to allow their RTRS video recordings to be used for educational purposes.

### **9.6.1. Screening (Days -21 to -2)**

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

- Obtain informed consent.
- Assess inclusion/exclusion criteria.
- Collect medical history.
- Perform a physical examination (including height and weight).
- Collect vital signs, including orthostatic systolic and diastolic blood pressures, orthostatic pulse rate, respiratory rate, and body temperature.
- Perform 12-lead ECG in triplicate (1 to 3 minutes apart).
- Perform a serum pregnancy test ( $\beta$ -hCG) only for female subjects of childbearing potential.
- Collect blood sample for serology testing (HIV-Ab, HBsAg, and HCV-Ab).
- Collect blood sample for hematology and clinical chemistry.
- Collect urine sample for urinalysis.
- Perform alcohol breathalyzer test and urine drug screen.
- Administer the YGTSS, including video recording.
- Video record subjects for the RTRS.
- Administer the PUTS.
- Administer the CGI-Tics – Severity scale.
- Administer the C-SSRS (Screening/Baseline version).
- Administer the Y-BOCS and SIGH-D-17.
- AE monitoring.
- Record prior medications.

All screening procedures must be completed and results evaluated by the investigator before the baseline procedures are performed on Day -1.

The following items will also be conducted at screening:

- Instruct subjects of childbearing potential who do not practice total abstinence to continue using contraception (see [inclusion criterion #10 in Section 8.1](#)).
- Eligible subjects will be instructed to return to the center on Day -1.

### **9.6.2. Baseline (Day -1)**

Subjects will return to the center on Day -1.



On Day -1, the following study evaluations and procedures will be performed at the study center:

- Update subject's eligibility.
- Update medical history.
- Perform a physical examination and weight.
- Collect vital signs, including orthostatic systolic and diastolic blood pressures, orthostatic pulse rate, respiratory rate, and body temperature.
- Perform 12-lead ECG in triplicate (1 to 3 minutes apart).
- Perform a urine pregnancy test for female subjects of childbearing potential.
- Collect blood sample for hematology and clinical chemistry.
- Collect urine sample for urinalysis.
- Perform alcohol breathalyzer test and urine drug screen.
- Collect blood sample for CYP2D6 genotype status.
- Collect blood sample for serum prolactin.
- Administer the YGTSS, including video recording.
- Video record subjects for the RTRS.
- Administer the PUTS.
- Administer the CGI-Tics – Severity scale
- Administer the C-SSRS (Since Last Visit version).
- Administer the ESRS-A.
- Administer the Y-BOCS and SIGH-D-17.
- Access the IWRS to obtain randomization assignments for eligible subjects.
- Dispense a 2-week supply of study drug and provide instructions on storage and administration of the study drug. Note: The NBI-98854 80 mg dose will be titrated in a blinded fashion (subjects will receive 40 mg for the first week followed by 80 mg).
- Instruct subjects to take study drug daily with a standard breakfast between 0700 and 1000 hours throughout the double-blind treatment period. (The timing of drug administration should remain consistent throughout the treatment period.)
- Instruct subjects to record the date and time of each dose in the space provided on the study drug kit.
- Instruct subjects to return to the study center at Week 2 ( $\pm 3$  days) and to return all empty study drug packaging and unused study drug.
- AE monitoring.
- Record concomitant medications.

The following will also be conducted before subjects may leave the study center:

- Instruct subjects of childbearing potential who do not practice total abstinence to continue using contraception (see [inclusion criterion #10 in Section 8.1](#)).



- Instruct subjects to notify the investigator by telephone if they experience any AEs and before taking any new concomitant medications.

### **9.6.3. Treatment Period: Weeks 2, 4, 6, and 8 ( $\pm 3$ days for each visit)**

Subjects will report to the study center at Weeks 2, 4, 6, and 8.

At Weeks 2, 4, 6, and 8 the following study evaluations and procedures will be performed at the study center:

- Perform a physical examination and weight.
- Collect vital signs, including orthostatic systolic and diastolic blood pressures, orthostatic pulse rate, respiratory rate, and body temperature.
- Perform 12-lead ECG in triplicate (1-3 minutes apart).
- Perform a urine pregnancy test for female subjects of childbearing potential.
- Collect blood sample for hematology and clinical chemistry.
- Collect urine sample for urinalysis.
- Collect blood sample for serum prolactin.
- Collect PK blood sample for NBI-98854 and metabolite concentrations.
- Administer the YGTSS, including video recording.
- Video record subjects for the RTRS.
- Administer the PUTS.
- Administer the CGI-Tics–Severity scale
- Administer the CGI-TS–Improvement scale.
- Administer the C-SSRS (Since Last Visit version).
- Administer the ESRS-A.
- Administer the Y-BOCS and SIGH-D-17.
- Dispense a 2-week supply of study drug (Weeks 2, 4, and 6 only).
- Perform compliance check by counting the capsules returned.
- AE monitoring.
- Record concomitant medications.

The following will also be conducted before subjects may leave the study center:

- Instruct subjects of childbearing potential who do not practice total abstinence to continue using contraception (see [inclusion criterion #10 in Section 8.1](#)).
- Instruct subjects to notify the investigator by telephone if they experience any AEs and before taking any new concomitant medications.

At any time, if the subject is unable to tolerate their current dose, the investigator may decrease the subject's dose. The investigator is allowed to reduce the subject's dose only one time during the study. Subjects who have had a dose reduction and are unable to tolerate their new dose will be discontinued from the study. To maintain the study blind, subjects receiving 40 mg

or placebo who have a dose reduction will continue to receive their current dose and subjects receiving 80 mg will be reduced to 40 mg.

#### **9.6.4. Follow-up Visit: Week 10 ( $\pm 3$ days) or Early Termination**

At Week 10 (or upon early termination) the following procedures will be performed at the study center:

- Perform a physical examination and weight.
- Collect vital signs, including orthostatic systolic and diastolic blood pressures, orthostatic pulse rate, respiratory rate, and body temperature.
- Perform 12-lead ECG in triplicate (1-3 minutes apart).
- Perform a urine pregnancy test for female subjects of childbearing potential.
- Collect blood sample for hematology and clinical chemistry.
- Collect urine sample for urinalysis.
- Collect blood sample for serum prolactin.
- Collect PK blood sample for NBI-98854 and metabolite concentrations.
- Administer the YGTSS including video recording.
- Video record subjects for the RTRS.
- Administer the PUTS.
- Administer the CGI-Tics – Severity scale
- Administer the CGI-TS – Improvement scale.
- Administer the C-SSRS (Since Last Visit version).
- Administer the ESRS-A.
- Administer the Y-BOCS and SIGH-D-17.
- AE monitoring.
- Record concomitant medications.
- For subjects who discontinue on or before Week 8, collect plasma sample for PK (early termination).
- Instruct subjects to continue using contraception until 30 days after the last dose of study drug (see criteria in [Section 8.1](#)).

#### **9.7. Study Duration**

The expected duration of study participation for each subject is approximately 13 weeks, including up to 21 days of screening, an 8-week double-blind treatment period, and a 2-week drug-free follow-up period.

## **9.8. Prohibitions and Restrictions**

### **9.8.1. Prior and Concomitant Medications**

The following medications are prohibited from 30 days before screening (unless otherwise stated) until follow-up visit (Week 10 or early termination) as described below:

- 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, phenytoin, phenobarbital, rifabutin, rifampin, primidone, St. John's Wort, carbamazepine) are prohibited.
- Dopamine agonists and precursors: Dopamine receptor agonists (eg, ropinirole) and precursors (eg, carbidopa/levodopa) are prohibited.
- Dopamine antagonist: Dopamine antagonists (eg, pimozide, haloperidol, aripiprazole, risperidone, clozapine, olanzapine, ziprasidone) are prohibited.
- Monoamine oxidase inhibitors (MAOIs): All MAOIs (eg, isocarboxazid, phenelzine, selegiline, tranylcypromine) are prohibited.
- VMAT-2 Inhibitors: VMAT-2 inhibitor medications (eg, tetrabenazine, reserpine) are prohibited, except for study drug.
- As needed (prn) use: As needed use of the following medications is strictly prohibited: anticholinergics, benzodiazepines, antipsychotics, psychostimulants, mood stabilizers, antidepressants, opiates, strong CYP3A4 inhibitors, and strong CYP2D6 inhibitors.

### **9.8.2. Dietary Restrictions**

Subjects are not permitted to consume more than 6 caffeine-containing beverages a day.

Grapefruit juice or grapefruit products are prohibited from 7 days before Day -1 until the follow-up visit. Foods containing poppy seeds are prohibited from 7 days before screening until the follow-up visit. Moderate alcohol consumption (1 to 2 drinks per day or 7 to 14 drinks per week) is allowed from 48 hours before Day 1 until the follow-up visit.

### **9.8.3. Other Restrictions**

Excessive use of tobacco and other products containing nicotine (including nicotine gum and patches) are prohibited during the study (ie, from 30 days before screening to the follow-up visit or early termination). Strenuous activity beyond what is customary for the subject is prohibited during the study.

Subjects must agree not to donate blood during the study, including the screening period, and for 4 weeks after completion of the study. Male subjects must agree to refrain from donating sperm for 90 days after the last dose of study drug.

Subjects must not have initiated CBIT during the screening period or at baseline (Day -1) or plan to initiate CBIT during the study.

## 9.9. Withdrawal Criteria

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

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

- If the type, frequency, or severity of any AE becomes unacceptable/intolerable.
- If the subject is unable to tolerate the starting dose or resumption of the previous dose.
- QTcF value >500 msec (cardiologist verified).
- 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.
- Subject is confirmed to be pregnant.

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

- Develops a clinically significant laboratory (eg, ALT or AST  $\geq 2.5$  times ULN) or ECG abnormality.
- Requires a medication that is prohibited by the protocol (refer to [Section 9.8.1](#)).
- Is non-compliant with the dosing regimen (<80% dosing compliance) as verified by drug accountability (Refer to [Section 10.6](#)).

All subjects prematurely discontinuing the study, regardless of cause, must have all early termination assessments performed (see [Section 9.6.4](#)).

### 9.9.1. Handling of Withdrawals

If a subject prematurely withdraws from the study 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.

### 9.9.2. Sponsor's Termination of Study

Neurocrine Biosciences, Inc. (NBI) reserves the right to discontinue the study at any time for clinical or administrative reasons.

Such a termination must be implemented by the investigator, if instructed to do so by NBI in a time frame that is compatible with the subjects' well-being.

## **10. STUDY DRUG**

### **10.1. Study Drug Supplies**

NBI or its designee will provide the study centers with subject-specific, study drug kits sufficient for the completion of the treatment period of the study together with the corresponding certificates of analysis.

NBI-98854 will be supplied as capsules containing 40 mg of NBI-98854 (free base); and matching placebo 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 Capsugel shells. The placebo capsules will appear identical to the NBI-98854 capsules.

### **10.2. Study Drug Storage**

NBI-98854 and placebo capsules must be stored at controlled room temperature (CRT) (20°C to 25°C or 68°F to 77°F) under the conditions specified in the Investigator's Brochure and in a locked area accessible only to the pharmacist (or designee) until dispensing. Excursions outside this range will be allowed provided they meet the following conditions:

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

### **10.3. Study Drug Packaging and Labeling**

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

Study drug will be supplied as capsules in child-resistant blistercard dispensers; each blistercard contains enough study drug for 14 days of dosing plus 3 extra dose days. The blistercards will contain capsules of NBI-98854 40 mg or matching placebo.

Double-dummy study drug administration:

Study drug will be administered in a double-dummy fashion throughout the 8-week double-blind treatment period. All subjects will receive two capsules for each day of dosing as described below:

- Subjects randomized to NBI-98854 40 mg will receive one 40 mg capsule and one matching placebo capsule.
- Subjects randomized to receive NBI-98854 80 mg will receive 40 mg (as one 40 mg capsule and one matching placebo capsule) for 7 days (for dose titration) and NBI-98854 80 mg (as two 40 mg capsules) for the remaining 7 days plus 3 extra dose days. Subjects will then receive two 40 mg capsules for each subsequent day of dosing.

- Subjects randomized to placebo will receive two matching placebo capsules.

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, expiration date, storage condition and the statement “Caution – New Drug: Limited by Federal (or US) Law to Investigational Use.”

#### **10.4. Blinding**

This study includes an 8-week double-blind placebo-controlled treatment period during which the subject, investigator, all study site personnel, the external video reviewer for the YGTSS interview, the RTRS video rater, and the Sponsor will be blinded to the subject’s treatment. During this treatment period, all subjects will receive NBI-98854 (doses of 40 mg or 80 mg), or placebo as two capsules (identical in appearance) to be self-administered once daily.

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

#### **10.5. Study Drug Administration**

Study drug will be self-administered once daily in the morning (between 0700 and 1000 hours) at home with a standard breakfast and must swallow it with at least 4 oz. of water every day for the 8-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 will record the date and time of study drug dosing each day on the form provided as part of the study drug packaging.

#### **10.6. Drug Compliance and Accountability**

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

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

#### **10.7. Study Drug Return**

Written documentation to account for study drug and study drug materials is mandatory; all unused study drug and study drug materials must be kept in a secure location for final

accountability and reconciliation. Returned study drug and study drug material must be accounted for on a study drug return form provided by NBI or designee. The investigator must provide a written explanation for any destroyed or missing study drug or study drug materials.

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

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

## **11. ADVERSE EVENTS**

All AEs, whether observed by the investigator, reported by the subject, noted from laboratory findings, or identified by other means, will be recorded from the time the subject signed the ICF until the subject's follow-up visit (Week 10 or early termination).

### **11.1. 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 TS symptoms, unless worsened from baseline

- Pregnancy

## 11.2. Intensity of Adverse Events

Adverse events must be graded for intensity. An intensity category of mild, moderate, or severe, as defined in Table 3, 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 3: Intensity of Adverse Events**

Grade	Intensity
<b>Mild</b>	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.
<b>Moderate</b>	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.
<b>Severe</b>	An AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

## 11.3. Relationship to Study Drug

The investigator will document his/her opinion of the relationship of the AE to treatment with study drug using the criteria outlined in Table 4. 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 4: Relationship of Adverse Events to Study Drug**

Relationship	Description
<b>Definite</b>	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.
<b>Possible</b>	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.
<b>Unlikely</b>	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.
<b>Not Related</b>	Any event that does not meet the above criteria.

## 11.4. Recording Adverse Events

For randomized subjects, each AE will be listed as a separate entry on an AE eCRF. Screen failure subjects will have AE information noted 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 11.6).
- Pregnancy (refer to [Section 11.7](#)).
- 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.

## **11.5. Post-Study Follow-Up of Adverse Events**

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

Adverse events ongoing at the follow-up 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.

## **11.6. Serious Adverse Events**

All SAEs will be recorded from the time the subject has signed the ICF until 30 days after the last dose of study drug.

### **11.6.1. Definition of a Serious Adverse Event**

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

- Death.
- A life threatening 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 preexisting condition that did not worsen during the clinical investigation is not considered an AE. Hospitalization or nursing home admission for the purpose of caregiver respite is not considered an AE. Complications that occur during hospitalization are AEs, and if a complication prolongs hospitalization, the event is considered serious. Treatment in a hospital emergency room is not a hospitalization.
- A persistent or significant incapacity or substantial disruption of a person's ability to conduct normal life functions.
- A congenital anomaly/birth defect.

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

#### **11.6.2. Managing Serious Adverse Events**

Subjects experiencing an SAE or an emergency situation will be examined by a physician as soon as possible. The physician in attendance will do whatever is medically needed for the safety and well-being of the subject. The subject will remain under observation as long as medically indicated. Appropriate laboratory studies will be conducted until all parameters return to normal or are otherwise explained or stable. The subject will be followed until the SAE resolves or until the subject is medically stabilized. The investigator (or designee) will notify the 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, an investigator becomes aware of an SAE, then the event must be documented and reported as described in Section 11.6.3.

#### **11.6.3. Reporting Serious Adverse Events and Other Immediately Reportable Events**

Serious AEs and other immediately reportable events (defined in [Section 11.4](#)) must be reported within 24 hours of first knowledge of the event by study personnel to the NBI medical monitor or NBI Clinical Drug Safety (CDS) Department. Reports of SAEs or pregnancies should be followed by a fax or email of the SAE or Pregnancy Form. It is important that the investigator 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: (866) 626-7792 or (858) 617-7792**

**CDS facsimile: (888) 617-7551**

**CDS e-mail: [cds@neurocrine.com](mailto:cds@neurocrine.com)**

**NBI Medical Monitor: Telephone: (858) 617-7250**

**Cell phone: (858) 431-6012**

#### **11.6.4. Expedited Safety Reports**

Neurocrine Biosciences, Inc. or its representatives will submit an Expedited Safety Report for any suspected adverse reaction (as defined in [Section 11.3](#)) that is considered both serious and unexpected within 15 calendar days and for any unexpected fatal or life threatening experience within 7 calendar days 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.

### **11.7. Pregnancy**

Pregnancy is neither an AE nor an SAE unless the criteria for an SAE are met. However, all pregnancies in female subjects who received 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 #10 in Section 8.1](#)) until 30 days after the last dose of study drug. If at any time between the time the subject signs the ICF and the last study visit a subject believes she is pregnant, the subject will be instructed to stop taking the study medication and return to the study center within 24 hours and undergo a serum pregnancy test to confirm pregnancy.

All confirmed pregnancies, in subjects who received study drug, must be immediately reported to NBI (refer to [Section 11.6.3](#) for contact information), followed by fax or email 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).

## **12. DOCUMENTATION OF DATA**

### **12.1. Case Report Form**

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

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

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

eCRF entries. The Principal Investigator will review the eCRFs for completeness and accuracy and enter his or her electronic signature on the eCRFs as evidence thereof.

Medidata will provide access to the 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.

## **12.2. Data Capture, Review, and Validation**

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

## **12.3. Coding Dictionaries**

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).

# **13. STATISTICAL AND ANALYTICAL PLAN**

Descriptive and inferential statistical methods will be used to evaluate and summarize the data from this study. The term "descriptive statistics" refers to the number of subjects (n), mean, median, standard deviation (SD), standard error of the mean (SEM), minimum, and maximum for continuous and ordinal categorical variables; and refers to the number and percentage of subjects for categorical variables. The term "inferential statistics" refers to hypothesis tests which will be performed to assess differences between each NBI-98854 treatment group and placebo for selected efficacy variables.

The primary efficacy endpoint in this study is the YGTSS TTS mean change from baseline (Day -1) to Week 8. Inferential statistics will be calculated for this endpoint as well as for other (secondary) efficacy endpoints, which include the YGTSS Global Tic Severity score mean change from baseline to Week 8, the RTRS total score mean change from baseline to Week 8, the PUTS total score mean change from baseline to Week 8, and the CGI-TS-Improvement mean score change from baseline to Week 8, and the CGI-Tics-Severity mean score change

from baseline to Week 8. Exploratory analyses of the Week 2, Week 4, and Week 6 values of these endpoints will be performed also. Nominal two-sided p-values will be reported for all hypothesis tests (ie, without any adjustments for multiplicity).

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

### **13.1. Analysis Sets**

Three analysis sets will be defined for this study. The safety analysis set will include all subjects who are randomized to a treatment group and receive at least one dose of study drug. The intent-to-treat (ITT) analysis set will include all subjects in the safety analysis set who have at least one evaluable TTS during the 8-week double-blind treatment period. The per-protocol (PP) analysis set will include all subjects in the ITT analysis set who have no efficacy-related important protocol deviations. Additional PP analysis set criteria may be specified in the SAP.

### **13.2. Sample Size**

The study sample size of 30 subjects per treatment group is based on a power calculation for the TTS change from baseline using a two-sample t-test with a two-sided Type I error of 0.05. This sample size provides 80% power to detect an effect size of approximately 0.75 and 90% power to detect an effect size of approximately 0.85. Note that the effect size is defined as an NBI-98854 treatment group vs. placebo mean difference divided by the common SD.

Effect sizes for the TTS from published reports of placebo-controlled TS trials generally range from approximately 0.6 to slightly greater than 1.0 ([Jankovic et al, 2010](#), [Yoo et al, 2013](#), [ClinicalTrials NCT01727700](#)). The effect sizes of 0.75 and 0.85 mentioned in the above paragraph are representative of effect sizes seen in clinical studies with other drugs being evaluated for the treatment of TS.

### **13.3. Handling of Missing Data**

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

### **13.4. Enrollment and Disposition of Subjects**

The summary of subject enrollment and disposition will display the number of subjects who were randomized to each treatment group, who received at least one dose of study drug, who completed the 8-week 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.

### **13.5. Demographics and Baseline Characteristics**

Demographic data (age, gender, race, and ethnicity) and baseline characteristics (including height, weight, BMI, CYP2D6 genotype status, age at TS diagnosis, and baseline values for the TTS score) will be summarized with descriptive statistics for each treatment group and for the overall study population. Medical history will also be summarized.

### **13.6. Study Drug Dosing and Compliance**

The number of doses of study drug taken during the double-blind, placebo-controlled treatment period will be summarized with descriptive statistics by visit (Weeks 2, 4, 6, and 8). The cumulative estimated number of doses taken through Week 8 will be summarized as well. Additionally, the number of dose reductions will be summarized.

### **13.7. Pharmacokinetic Data**

The plasma concentrations of NBI-98854 and the metabolite NBI-98782 will be summarized with descriptive statistics by visit (Weeks 2, 4, 6, 8, and 10). Concentrations below the lower limit of quantification will be set equal to zero for all plasma concentration summaries.

### **13.8. Efficacy Data**

The efficacy measures in this study include the YGTSS, RTRS, PUTS, CGI-Tics-Severity, and CGI-TS-Improvement. A number of derived variables based on these measures (eg, the TTS) will be summarized with descriptive statistics by visit, and inferential statistics will be calculated for selected variables as described in the following paragraphs. The SAP will provide a full description of the derived variables that will be summarized for these efficacy measures.

The TTS changes from baseline (Day -1) and the Global Tic Severity score changes from baseline (Day -1) at Weeks 2, 4, 6, and 8 will be analyzed with a mixed-effects model repeated measures (MMRM) model which includes the baseline value as a covariate and treatment group (placebo, NBI-98854 40 mg, or NBI-98854 80 mg), visit (Week 2, 4, 6, or 8), treatment group by visit interaction, and baseline by visit interaction as fixed effects. Subject will be included as a random effect.

Least-squares (LS) mean differences between each NBI-98854 treatment group and placebo at each visit will be tested for significance and summarized with 2-sided 95% confidence intervals. Nominal 2-sided p-values will be reported for all hypothesis tests. Note that the primary comparisons of interest are those for the Week 8 visit; comparisons at Weeks 2, 4, and 6 are considered to be exploratory.

Similar MMRM analyses will be performed for the RTRS total score and PUTS total score.

The CGI-Tics – Severity and CGI-TS-Improvement will be summarized by visit with both continuous variable descriptive statistics (using numeric scores which range from 1 through 7) and with frequency tables (based on the response category descriptors). Additionally, the percentage of subjects who are “Much Improved” or “Very Much Improved” on the improvement scale will be summarized.

Hypothesis tests comparing each NBI-98854 treatment group to placebo at Weeks 2, 4, 6, and 8 will be performed for the numeric CGI-Tics – Severity and CGI-TS-Improvement scores using an MMRM model similar to the model described above for the TTS, but without a baseline covariate.

The descriptive and inferential statistical summaries for the efficacy variables will be presented for both the ITT and PP analysis sets.

### **13.9. Safety Data**

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

Summary tables will be presented including all TEAEs, only TEAEs that are considered to be possibly or definitely related to study drug, and TEAEs according to maximum intensity.

Additional summaries will be presented for TEAEs leading to premature discontinuation from the study, SAEs, and deaths.

Clinical laboratory, serum prolactin, vital signs, ECG, C-SSRS, ESRS-A, Y-BOCS, and SIGH-D-17 data will be summarized by visit with descriptive statistics. Clinically significant physical examination findings will be displayed in a data listing. Prior and concomitant medications will also be summarized.

### **13.10. Software**

Statistical calculations and summaries will be generated using SAS software version 9.3 or later.

### **13.11. Interim Analysis**

An interim analysis is not planned for this study.

## **14. REGULATORY AND ETHICAL ISSUES**

### **14.1. General Legal References**

The study will be carried out according to the provision of the US CFR, the US FDA, and the International Conference on Harmonisation Guidelines (ICH) 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.

### **14.2. Institutional Review Board**

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

### **14.3. Protocol Adherence and Amendments**

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

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

#### **14.4. Required Documents**

The investigator must provide to NBI or its representatives the following documents before the enrollment of any subject (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).
- 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.

#### **14.5. Informed Consent**

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

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

#### **14.6. Study Monitoring**

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

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



#### **14.7. Quality Assurance**

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

#### **14.8. Record Retention**

Federal regulations require that records of drug disposition, 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.

#### **14.9. Confidentiality**

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

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

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

### **15. STUDY COMMENCEMENT AND DISCONTINUATION**

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

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

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