CLINICAL STUDY PROTOCOL

An Open-Label, Safety and Tolerability Study of NBI-98854 for the Treatment of Subjects With Tourette Syndrome

Amendment No. 3 Final Version Date: 01 March 2017

Amendment No. 2 Final Version Date: 22 June 2016

Amendment No. 1 Final Version Date: 12 May 2016

Original Final Version Date: 08 April 2016

Study No.: NBI-98854-1601

Development Phase: Phase 2

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

SIGNATURES:

I agree to conduct this study in accordance with the requirements of this clinical study protocol and also in accordance with the following:

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

CLINICAL STUDY TITLE:

An Open-Label, Safety and Tolerability Study of NBI-98854 for the Treatment of Subjects With Tourette Syndrome

PROTOCOL No.: NBI-98854-1601

As Agreed:

_____ _____

Principal Investigator Signature Date

PRINCIPAL INVESTIGATOR:

_____

(Print Principal Investigator Name)

SITE:

_____

(Print Site Name)

Accepted for the Sponsor:

SPONSOR:

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

02 MAR 2017
Date

[redacted]

LIST OF SPONSOR PERSONNEL

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

Medical Monitor: [redacted]
Telephone: [redacted]
Facsimile:
Cell Phone:

Vice President, Clin c Development: [redacted]
Telephone: [redacted]
Facsimile:

Serious Adverse Event Reporting:
Telephone: [redacted]
Facsimile:
Email:

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

2. SYNOPSIS

Protocol Title: An Open-Label, Safety and Tolerability Study of NBI-98854 for the Treatment of Subjects With Tourette Syndrome

Protocol Number: NBI-98854-1601

Study Centers: Approximately 60 study sites in the United States.

Objective:

To evaluate the safety and tolerability of NBI-98854 (titrated from 10 mg to 20 mg in children, 20 mg to 40 mg in adolescents, and 40 mg to 80 mg in adults) administered once daily for up to 24 weeks for the treatment of Tourette Syndrome (TS).

Study Design:

This is a Phase 2, open-label, fixed-dose titration study to evaluate the safety and tolerability of NBI-98854 administered once daily for a total of 24 weeks in children, adolescents, and adults with TS. NBI-98854 doses will be titrated from 10 mg to 20 mg in children (6 to 11 years of age), 20 mg to 40 mg in adolescents (12 to 17 years of age), and 40 mg to 80 mg in adults (18 to 64 years of age). Up to 180 male and female subjects (up to 90 pediatric subjects [ie, children and adolescents] and up to 90 adult subjects) with a clinical diagnosis of TS will be enrolled.

Parental or legal guardian informed consent with signed and witnessed pediatric assent for pediatric subjects or informed consent for adult subjects must be obtained prior to conduct of any study-related procedures. Subjects will also be asked to sign an optional release form to allow their Rush Video-based Tic Rating Scale (RTRS) recordings to be used for educational purposes.

Subjects who have their final Phase 2 study (NBI-98854-1501 or NBI-98854-1505) visit >30 days prior to anticipated baseline (Day -1) require screening. These subjects will be screened to determine eligibility within 20 days (Days -21 to -2) before baseline (Day -1). At baseline (Day -1), eligible subjects will return to the study site for collection of baseline safety and efficacy assessments.

Subjects can have their final Phase 2 study (NBI-98854-1501 or NBI-98854-1505) visit on the same day as baseline (Day -1) for this study provided this study's informed consent, and assent (if applicable), is obtained before the final NBI-98854-1501 or NBI-98854-1505 visit. This will allow certain pharmacodynamic (PD) and safety assessments to be used for both the previous study and the current study.

On Day -1, all subjects will have baseline study assessments conducted and be assessed for eligibility. Eligible subjects will receive a supply of NBI-98854 (10, 20, or 40 mg, based on their age group) for the first 4 weeks of treatment. Beginning on Day 1, subjects will take study drug once daily at home at approximately the same time each day (under the supervision of the subject's parent/legal guardian for pediatric subjects) throughout the 24-week treatment period.

At the end of Week 4, the investigator may escalate the NBI-98854 dose from 10 to 20 mg in children, from 20 to 40 mg in adolescents, and from 40 to 80 mg in adults, or continue with the subject's current dose for the remainder of the treatment period. A dose escalation will be allowed if (1) the investigator or designee's assessment of the Clinical Global Impression of Improvement-Tourette Syndrome (CGI-TS) is "minimally improved", "not changed", "minimally worse", "much worse", or "very much worse", and (2) the safety and tolerability of the current dose is acceptable as determined by a physician. The subject will then continue at this dose until the end of the treatment period (ie, the end of Week 24).

At any time after dose escalation, the investigator may modify the timing of study drug dosing (eg, qam to qhs) and/or decrease a subject's dose (to 10 mg for children, 20 mg for adolescents, or 40 mg for adults) if the subject is unable to tolerate the dose increase. Subjects who are unable to tolerate the starting dose of 10 mg for children, 20 mg for adolescents, 40 mg for adults, or the resumption of the 10 mg, 20 mg, or 40 mg dose following a tolerability issue after the dose escalation at Week 4, will be discontinued from the study.

Subjects will return to the study site every 4 weeks during the treatment period, at the end of Weeks 4, 8, 12, 16, 20, and 24. As much as possible, these visits should occur at approximately the same time of day. For pediatric subjects only, the study site will call the subject or parent/legal guardian at study Week 2 and Week 6 to inquire about any study drug-related issues related to compliance or tolerability.

A follow-up visit will be performed at the end of Week 28 (4 weeks after the last dose of study drug) or early termination. Subjects who withdraw from the study at any time during the treatment period will be asked to

complete an early termination visit within 4 weeks. Safety, PD, and pharmacokinetics (PK) will be assessed at scheduled times throughout the study. The treatment period visits (end of Weeks 4, 8, 12, 16, 20, and 24) and the follow-up visit (end of Week 28) will have a visit window of ±6 days.
Study Population: This study will be conducted in up to 180 male and female subjects with a Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV or -V diagnosis of TS. A total of up to 90 pediatric subjects (6 to 17 years of age [inclusive]) and up to 90 adult subjects (18 to 64 years of age [inclusive]) will be enrolled into this study. This study will only enroll subjects who had previously participated in and completed the NBI-98854-1501 or NBI-98854-1505 study and express an interest in continuing to receive or re-initiate NBI-98854.
Duration of Treatment and Study Participation: The expected duration of study participation for each subject is up to 31 weeks, including a 3-week screening period, a 24-week treatment period, and a 4-week follow-up period.
Investigational Product, Dose, and Mode of Administration: NBI-98854 will be supplied as capsules containing 10 mg, 20 mg, or 40 mg of NBI-98854 (free base). The NBI-98854 80 mg dose will be administered as two 40 mg capsules. The NBI-98854 capsules will be taken with at least 4 oz. of water.
Reference Therapy, Dose, and Mode of Administration: Not applicable.
Criteria for Evaluation: **Pharmacodynamics:** The following PD assessments will be administered at baseline (Day -1), at the end of Weeks 4, 8, 12, 16, 20, and 24, and at the follow-up visit (the end of Week 28, or early termination): All subjects: • Yale Global Tic Severity Score (YGTSS) • Rush Video-based Tic Rating Scale • Premonitory Urge for Tics Scale (PUTS) • Clinical Global Impression (CGI)-Tics Severity Pediatric subjects only: • Pediatric Quality of Life Inventory (PedsQL) Adult subjects only: • Gilles de la Tourette Syndrome-Quality of Life (GTS-QOL) The CGI-TS (assessed by the investigator) and Patient Global Impression of Change-Tourette Syndrome (PGIC-TS) scales will be administered at the end of Weeks 4, 8, 12, 16, 20, and 24, and at the follow-up visit (the end of Week 28 or upon early termination) in all subjects.

Criteria for Evaluation (continued):

Plasma Drug Exposure: Blood samples to evaluate plasma concentrations of NBI-98854, and the metabolite NBI-98782, will be collected during the treatment period (end of Weeks 4, 8, 12, 16, 20, and 24), and at the follow up visit (end of Week 28, or early termination).

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

All subjects:

- Adverse events (AEs)
- Clinical laboratory tests (hematology, clinical chemistry, and urinalysis)
- Serum prolactin
- Hemoglobin A1c
- Vital signs (including orthostatic blood pressures and pulse, respiratory rate, and oral body temperature)
- Physical examinations (including height and weight)
- 12-lead electrocardiograms (ECGs)
- Columbia-Suicide Severity Rating Scale (C-SSRS) (pediatric version will be used for pediatric subjects)
- Extrapyramidal Symptom Rating Scale-Abbreviated (ESRS-A)

Pediatric subjects only:

- Children's Depression Rating Scale - Revised (CDRS-R), Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS), and Attention-Deficit Hyperactivity Disorder (ADHD) Rating Scale 5: Home Version

Adult subjects only:

- Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) and Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D-17)

If the final study visit for the previous study occurs on the same day as Day -1 of the current study, the PD assessments that can apply to both the previous study and the current study include the YGTSS, RTRS, PUTS, and CGI-Tics-Severity. The safety assessment results that can apply to both the previous study and the current study include physical examinations (including weight), vital signs, ECGs, ESRS-A, CY-BOCS, CDRS-R, Y-BOCS, and SIGH-D-17. Other Day -1 assessments (including safety labs) must be collected for the current study (even if the subject is completing the final visit for the previous study).

Statistical methods:

All safety, PK, and PD data will be summarized by treatment and timepoint (as appropriate) using descriptive statistics.

The PD measures in this study include the YGTSS-Total Tic Score (TTS) as scored by the certified site raters using Rater Station[sm], RTRS, PUTS, CGI-TS, PGIC-TS, CGI-Tics-Severity, PedsQL(pediatric subjects only), and GTS-QOL (adult subjects only).

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADHD	Attention-Deficit Hyperactivity Disorder
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
CBIT	Comprehensive Behavioral Intervention for Tics
CDRS-R	Children's Depression Rating Scale - Revised
CDS	Clinical Drug Safety
CFR	Code of Federal Regulations
CGI-Tics-Severity	Clinical Global Impression of Tics-Severity
CGI-TS	Clinical Global Impression of Improvement-Tourette Syndrome
C_{max}	Maximum plasma concentration
CRT	Controlled room temperature
C-SSRS	Columbia Suicide Severity Rating Scale
CY-BOCS	Children's Yale-Brown Obsessive-Compulsive Scale
CYP	Cytochrome P450
DSMB	Data Safety Monitoring Board
DSM-IV or -V	Diagnostic and Statistical Manual of Mental Disorders 4^{th} or 5^{th} Editions
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EDTA K_2	Dipotassium ethylenediaminetetraacetic acid
ESRS-A	Extrapyramidal Symptom Rating Scale-Abbreviated
FDA	[United States] Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GTS-QOL	Gilles de la Tourette Syndrome-Quality of Life Scale
HBsAg	Hepatitis B surface antigen
HCV-Ab	Hepatitis C virus antibody
HIV-Ab	Human immunodeficiency virus antibody
HR	Heart rate
HRQOL	Health-related quality of life
ICF	Informed consent form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
IWRS	Interactive Web Response System
MAOI	Monoamine oxidase inhibitor
MedDRA	Medical Dictionary for Regulatory Activities
NBI	Neurocrine Biosciences, Inc.
PD	Pharmacodynamic(s)
PedsQL	Pediatric Quality of Life Inventory
PGIC-TS	Patient Global Impression of Change-Tourette Syndrome
PK	Pharmacokinetic(s)

prn	As needed
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
SIGH-D-17	Structured Interview Guide for the Hamilton Depression Rating Scale
TEAE	Treatment-emergent adverse event
TD	Tardive dyskinesia
TS	Tourette Syndrome
TTS	Total Tic Score
UDS	Urine drug screen
ULN	Upper limit of normal
US	United States
VMAT2	Vesicular monoamine transporter 2
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 Practice (GCP). These standards respect the following guidelines:

- Good Clinical Practice: Consolidated Guideline (International Conference on Harmonisation [ICH] of Technical Requirements for the Registration of Pharmaceuticals for Human Use, May 1996).
- United States (US) Code of Federal Regulations (CFR) regulating 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) and assent forms are discussed in Section 14.

5. INTRODUCTION

5.1. Background

Tourette Syndrome (TS) is a disorder characterized by the presence of chronic motor and 1 or more vocal tics that often appear in childhood or early adolescence (American Psychiatric Association, 1994). 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 one 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 (ADHD), and impulsive or antisocial behavior (Chen et al., 2012; Felling and Singer, 2011).

Persistent tics can have a significant impact on quality of life and often lead to impaired psychosocial functioning. Some of these problems include, but are not limited to, social isolation, bullying, physical discomfort (with pain or injury), and poor academic performance (Roessner et al., 2013). Psychosocial stressors can, in turn, exacerbate tic symptomatology. It is under these conditions that pharmacological interventions may be considered (Chen et al., 2012; Shprecher and 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.

5.2. NBI-98854

NBI-98854 (valbenazine tosylate) is a highly selective, orally active VMAT2 inhibitor and is currently under development at NBI for the treatment of tardive dyskinesia (TD) and TS.

In nonclinical studies, NBI-98854 appears to cause little or no cytochrome P450 (CYP) enzyme inhibition or induction at pharmacologically relevant concentrations. Metabolism of NBI-98854 is characterized by hydrolysis of NBI-98854 to NBI-98782, and CYP3A4/5-dependent mono-oxidation to NBI-136110. All 3 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. NBI-98854 delivers NBI-98782 in a controlled fashion with limited peak-to-trough plasma concentration fluctuation and low pharmacokinetic (PK) variability that should limit adverse events (AEs) associated with excessive monoamine depletion. There was no evidence of teratogenicity in rats or rabbits.

Thirteen clinical studies with NBI-98854 have been completed to date: 9 Phase 1 studies, 8 in healthy male and female elderly and nonelderly subjects, and 1 in hepatically impaired adults; and 4 Phase 2 studies in subjects with TD and a clinical diagnosis of schizophrenia or schizoaffective disorder, mood disorder, or gastrointestinal disorder. In addition, preliminary data are available for the 6-week, placebo-controlled period for the ongoing Phase 3 study NBI-98854-1304 in subjects with TD and a clinical diagnosis of schizophrenia or schizoaffective disorder, or mood disorder. A total of 510 subjects have received at least 1 dose of NBI-98854 and 246 received placebo in these studies. Clinically and statistically significant reductions in TD symptoms have been demonstrated in the phase 2 and phase 3 clinical studies.

Clinical PK data indicate that when administered orally under fasted conditions, NBI-98854 appeared to be rapidly absorbed with maximum plasma concentration (C_{max}) being reached within 1 hour. An active metabolite, NBI-98782, was formed gradually with C_{max} typically being reached 4 to 10 hours after dosing. Plasma concentrations for both NBI-98854 and NBI-98782 appeared to decline after reaching maximal concentration and both exhibited an apparent terminal half-life of approximately 20 hours in non-elderly adult subjects and 23 to 28 hours in elderly subjects. Coadministration of ketoconazole (strong CYP3A4/5 inhibitor) with NBI-98854 caused an approximate 1.5- and 1.7-fold increase in C_{max} of NBI-98854 and NBI-98782, respectively. Coadministration of NBI-98854 and rifampin resulted in a decrease in systemic exposure to NBI-98854, a decrease in systemic exposure to NBI-98782, and an increase in C_{max} for NBI-136110, but a decrease in area under the plasma concentration versus time curve extrapolated to infinity ($AUC_{0-\infty}$) for NBI-136110.

NBI-98854 has been generally well tolerated in single doses up to 300 mg and in multiple doses of up to 100 mg. In Phase 2 studies and the interim analysis from one Phase 3 study, treatment-emergent adverse events (TEAEs) were reported by 42.8% and 36.4% of NBI-98854 and placebo subjects, respectively. AEs reported in ≥2% of NBI-98854 subjects and at a higher incidence than placebo included somnolence, headache, fatigue, vomiting, dry mouth, akathisia, and fall. Suicidal ideation was reported in a similar percentage of subjects receiving NBI-98854 or placebo (2.0% and 1.9%, respectively). Most TEAEs were mild or moderate in intensity.

Two deaths have been reported in clinical studies; 1 subject who received placebo died due to cardiopulmonary arrest secondary to myocardial infarction and the second subject died possibly due to a cardiovascular event (treatment remains blinded). No treatment-emergent serious AEs (SAEs) have been reported in Phase 1 studies. In Phase 2 studies and the interim analysis from one Phase 3 study, SAEs were reported in 17 subjects (4.9%) who received NBI-98854 and 6 subjects (2.8%) who received placebo. There were no clinically important differences in the number or types of SAEs reported across dose groups. Only 1 SAE (acute hepatitis) was 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.

Three NBI-98854 studies in subjects with TS are discussed in Section 5.3.

5.3. Study and Dose Rationale

All subjects in the current study will have previously received NBI-98854 10 mg to 80 mg for 6 to 8 weeks or placebo in a Phase 2 NBI-98854 study (NBI-98854-1501 or NBI-98854-1505). In the current study, subjects will receive a starting dose of NBI-98854 (10 mg in children [6 to 11 years of age], 20 mg in adolescents [12 to 17 years of age], and 40 mg in adults) once daily for 4 weeks. At the end of Week 4, the investigator may escalate the subject's dose (to 20 mg in children, 40 mg in adolescents, or 80 mg in adults) or continue with the subject's current dose. A dose escalation will be allowed at the end of Week 4 based on the physician investigator's (or designee's) assessments of the safety and tolerability of NBI-98854 as well as clinical impression of TS.

The initial Phase 1b, open-label, multiple-dose study of the safety, tolerability, PK, and pharmacodynamics (PD) of NBI-98854 (NBI-98854-1403) was conducted in 17 male and female adolescents with TS (12 to 18 years of age) and 11 male and female children with TS (6 to 11 years of age). Doses of NBI-98854 10 mg, 25 mg, or 50 mg were administered in adolescents, and doses of NBI-98854 5 mg and 10 mg were administered in children daily over a 14-day treatment period following a multiple ascending dose protocol. The dose strengths for Study NBI-98854-1403 were selected based on prior clinical experience with NBI-98854 in adult patients with a diagnosed hyperkinetic movement disorder, TD, as well as thorough PK modeling that specified body weight as a key covariate. Preliminary results from NBI-98854-1403 show that these doses have been well-tolerated in both child and adolescent age groups, and the observed plasma concentration measures of NBI-98854 and its metabolites in the subjects evaluated in both age groups are consistent with the a priori, PK model-based predictions of study drug exposure.

Study NBI-98854-1501 is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel group, dose-ranging study to evaluate the efficacy, safety, and tolerability of 2 doses of NBI-98854 (10 mg and 20 mg in children [6 to 11 years of age], and 20 mg and 40 mg in adolescents [12 to 17 years of age]) relative to placebo, administered once daily for 6 weeks in pediatric subjects with TS. Subjects within each age group will be randomized in a 1:1:1 ratio to placebo or 1 of the 2 NBI-98854 doses. This study opened to screening in March 2016.

Study NBI-98854-1505 is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy, safety, and tolerability of 2 doses of NBI-98854 (40 mg and 80 mg) relative to placebo, administered once daily for 8 weeks in adult subjects with TS. Subjects will be randomized in a 1:1:1 ratio to placebo or 1 of the 2 NBI-98854 doses. This study opened to screening in November 2015.

Rationale for Dose Selection

The doses used in this Phase 2 study reflect the doses that are being used in the ongoing Phase 2 placebo-controlled studies in pediatric and adult subjects with TS. The doses selected for the pediatric subjects are within the NBI-98854 dose range evaluated in Study NBI-98854-1403 and have been demonstrated to be safe and well-tolerated in the pediatric TS subjects dosed with NBI-98854 to date. The doses selected for the adult subjects are aligned with those selected for evaluation in the Phase 3 TD program.

6. STUDY OBJECTIVES

The objective of this clinical study is to evaluate the safety and tolerability of NBI-98854 (titrated from 10 mg to 20 mg in children, 20 mg to 40 mg in adolescents, and 40 mg to 80 mg in adults) administered once daily for up to 24 weeks for the treatment of TS.

7. OVERVIEW OF STUDY DESIGN

This is a Phase 2, open-label, fixed-dose titration study to evaluate the safety and tolerability of NBI-98854 administered once daily for a total of 24 weeks in children, adolescents, and adults with TS. NBI-98854 doses will be titrated from 10 mg to 20 mg in children (6 to 11 years of age), 20 mg to 40 mg in adolescents (12 to 17 years of age), and 40 mg to 80 mg in adults (18 to 64 years of age). Up to 180 male and female subjects (up to 90 pediatric subjects [ie, children and adolescents] and up to 90 adult subjects) with a clinical diagnosis of TS will be enrolled. The study will include approximately 60 study sites in the United States.

Parental or legal guardian informed consent with signed and witnessed pediatric assent for pediatric subjects or informed consent for adult subjects must be obtained prior to conduct of any study-related procedures. Subjects will also be asked to sign an optional release form to allow their Rush Video-based Tic Rating Scale (RTRS) recordings to be used for educational purposes.

Subjects who have their final Phase 2 study (NBI-98854-1501 or NBI-98854-1505) visit >30 days prior to anticipated baseline (Day -1) require screening. These subjects will be screened to determine eligibility within 20 days (Days -21 to -2) before baseline (Day -1).

Subjects can have their final Phase 2 study (NBI-98854-1501 or NBI-98854-1505) visit on the same day as baseline (Day -1) for this study provided that the NBI-98854-1601 informed consent, and assent (if applicable), is obtained before the final NBI-98854-1501 or NBI-98854-1505 visit. This will allow certain PD and safety assessments to be used for both the previous study and the current study. The PD assessments that can apply to both the previous study and the current study include the Yale Global Tic Severity Score (YGTSS), RTRS, Premonitory Urge for Tics Scale (PUTS), and Clinical Global Impression (CGI) of

Tics-Severity. The safety assessment results that can apply to both the previous study and the current study include physical examinations (including weight), vital signs, electrocardiograms (ECG), Extrapyramidal Symptom Rating Scale-Abbreviated (ESRS-A), Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS; pediatric subjects only), Children's Depression Rating Scale - Revised (CDRS-R; pediatric subjects only), Yale-Brown Obsessive-Compulsive Scale (Y-BOCS; adult subjects only), and the Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D-17; adult subjects only). All other Day -1 assessments (including safety labs) must be collected for the current study (even if the subject is completing the final visit for the previous study).

On Day -1, all subjects will have baseline study assessments conducted and be assessed for eligibility. Eligible subjects will receive a supply of NBI-98854 (10, 20, or 40 mg, based on their age group) for the first 4 weeks of treatment. Beginning on Day 1, subjects will take study drug once daily at home at approximately the same time each day (under the supervision of the subject's parent/legal guardian for pediatric subjects) throughout the 24-week treatment period.

At the end of Week 4, the investigator may escalate the NBI-98854 dose from 10 to 20 mg in children, from 20 to 40 mg in adolescents, and from 40 to 80 mg in adults, or continue with the subject's current dose for the remainder of the treatment period. A dose escalation will be allowed if (1) the investigator or designee's assessment of the Clinical Global Impression of Improvement -Tourette Syndrome (CGI-TS) is "minimally improved", "not changed", "minimally worse", "much worse", or "very much worse", and (2) the safety and tolerability of the current dose is acceptable as determined by a physician. The subject will then continue at this dose until the end of the treatment period (ie, the end of Week 24).

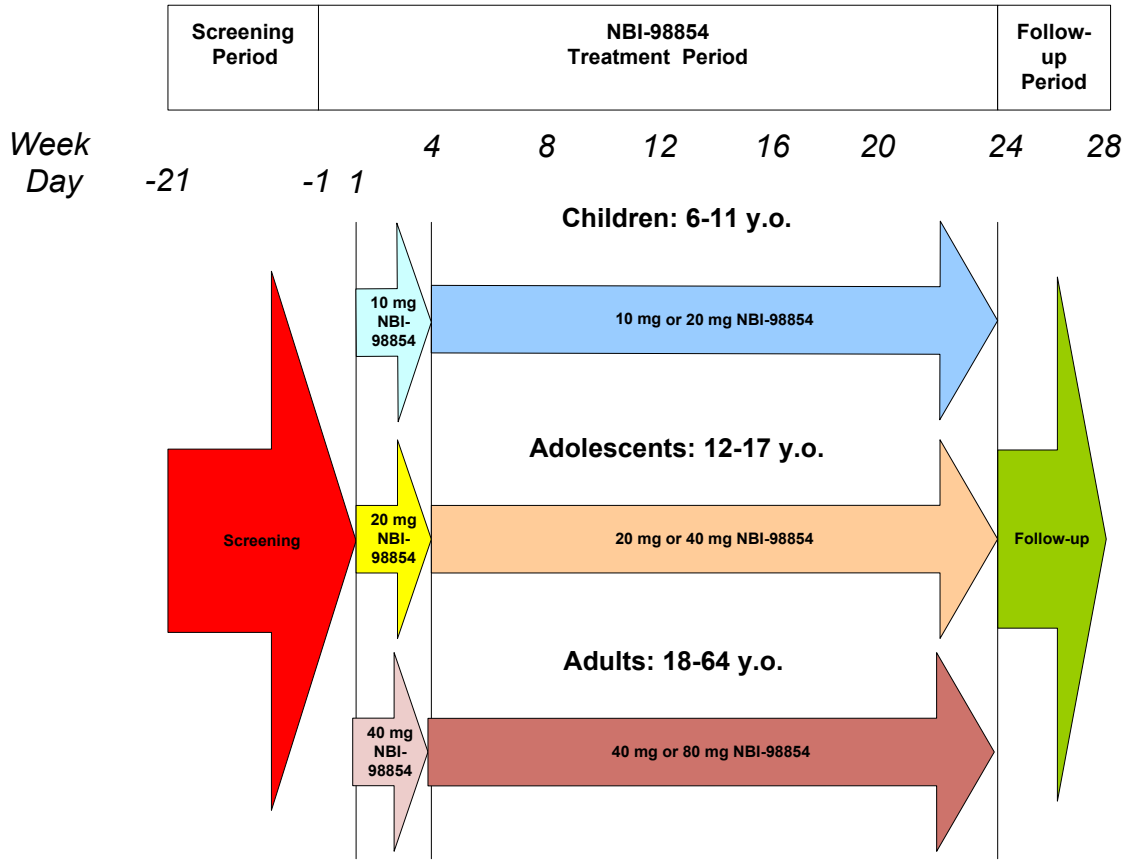
At any time after dose escalation, the investigator may modify the timing of study drug dosing (eg, qam to qhs) and/or decrease a subject's dose (to 10 mg for children, 20 mg for adolescents, or 40 mg for adults) if the subject is unable to tolerate the dose increase. Subjects who are unable to tolerate the starting dose of 10 mg for children, 20 mg for adolescents, 40 mg for adults, or the resumption of the 10 mg, 20 mg, or 40 mg dose after the dose escalation at Week 4, will be discontinued from the study.

Subjects will return to the study site every 4 weeks during the treatment period, at the end of Weeks 4, 8, 12, 16, 20, and 24. As much as possible, these visits should occur at approximately the same time of day. For pediatric subjects only, the study site will call the subject or parent/legal guardian approximately 2 weeks and 6 weeks after starting dosing (ie, at study Weeks 2 and 6) to inquire about any study drug-related issues with regard to compliance or tolerability.

A follow-up visit will be performed at the end of Week 28 (4 weeks after the last dose of study drug) or early termination. Subjects who withdraw from the study will be asked to complete an early termination visit within 4 weeks. Safety, PD, and PK will be assessed at scheduled times throughout the study. The treatment period visits (end of Weeks 4, 8, 12, 16, 20, and 24) and the follow-up visit (end of Week 28) will have a visit window of ±6 days.

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

Figure 1: Study Design Schematic



Subjects who enter the study within 30 days of completing NBI-98854-1501 or NBI-98854-1505 are not required to undergo screening and the first day of the study is Day -1 (baseline) for these subjects.

8. STUDY POPULATION

This study will be conducted in up to 180 male and female subjects with a Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV or -V diagnosis of TS. A total of up to 90 pediatric subjects (6 to 17 years of age [inclusive]) and up to 90 adult subjects (18 to 64 years of age [inclusive]) will be enrolled into this study. This study will only enroll subjects who had previously participated in and completed the NBI-98854-1501 or NBI-98854-1505 study and express an interest in continuing to receive or re-initiate NBI-98854. Subjects must meet all the inclusion criteria and none of the exclusion criteria in order to qualify for the study.

8.1. Inclusion Criteria

8.1.1. Inclusion Criteria for All Subjects

To participate in this study, subjects must:

1. Have documentation of written and witnessed assent from the subject and written informed consent from the subject's parent or legal guardian for pediatric subjects or have provided written informed consent for adult subjects.

2. Have participated in and completed the NBI-98854-1501 or NBI-98854-1505 Phase 2 study. Subjects can have their final NBI-98854-1501 or NBI-98854-1505 visit on the same day as Day -1 for this study provided the current study's informed consent, and assent (if applicable), is obtained before the final NBI-98854-1501 or NBI-98854-1505 visit.
3. Be male or female, aged 6 to 64 years, inclusive.
4. Be in good general health and expected to complete the study as designed.
5. Have a DSM-IV or -V diagnosis of TS.
6. Subjects with TS spectrum diagnoses (eg, obsessive-compulsive disorder [OCD], ADHD) must have a stable psychiatric status as clinically determined by the investigator at screening (if applicable) and at baseline (Day -1).
7. 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 nondopaminergic 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).
8. 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.
9. Subjects must use contraception consistently from baseline (Day -1) until 30 days after the last dose of study drug for female subjects and 90 days after the last dose of study drug for male subjects.

   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 baseline (Day -1).

   The following subjects are not required to use contraception:

   - Subjects who practice total abstinence from sexual intercourse as the preferred lifestyle (periodic abstinence is not acceptable).
   - Female subjects not of childbearing potential (ie, have not reached menarche, postmenopausal for at least 1 year prior to screening, or surgically sterile [bilateral oophorectomy, hysterectomy or bilateral tubal ligation] at least 3 months prior to

screening) or with male partners who have been vasectomized at least 3 months prior to screening.

- Male subjects not of child-producing potential (ie, have not reached spermarche or who have been vasectomized at least 3 months prior to screening) or with female partners not of childbearing potential (as listed above).

10. Female subjects of childbearing potential must have a negative urine pregnancy test at baseline (Day -1).
11. Be willing to provide authorization (adult subjects) or the subject's parent or legal guardian is willing to provide authorization (pediatric subjects) for access to personal health information in conjunction with US Health Insurance Portability and Accountability Act (HIPAA).
12. Be willing and able to adhere to the study regimen and study procedures described in the protocol and informed consent/assent forms, including all requirements at the study site and return for the follow-up visit.

8.1.2. Inclusion Criteria for Pediatric Subjects

In addition to the inclusion criteria for all subjects, the following criteria must be met for pediatric subjects (age 6 to 17 years of age [inclusive]):

13. Have a body weight (in kilograms [kg]) greater than or equal to the 5th percentile, but less than the 95th percentile of his/her age- and gender-matched weight percentile at baseline (Day -1).

8.1.3. Inclusion Criteria for Adult Subjects

In addition to the inclusion criteria for all subjects, the following criteria must be met for adult subjects (age 18 to 64 years of age [inclusive]):

14. Have a body mass index (BMI) of 18 to 40 kg/m^2 (inclusive) at baseline (Day -1). (BMI is defined as the subject's weight in kg divided by the square of the subject's height in meters.)

8.1.4. Inclusion Criteria for Adolescent and Adult Subjects

In addition to the inclusion criteria for all subjects, the following criteria must be met for adolescent and adult subjects (age 12 to 64 years of age [inclusive]):

15. Must have a negative urine drug screen ([UDS]; negative for amphetamines, barbiturates, benzodiazepine, phencyclidine, cocaine, opiates, or cannabinoids) at screening (if applicable) and at baseline (Day -1) (including results from UDS performed at the clinical site and UDS results from the central lab). At baseline (Day -1), results from the UDS performed at the clinical site will be used by the investigator to confirm eligibility. Subjects who are on stable doses of prescribed and supervised (not as needed [prn]) benzodiazepines, opiates, or psychostimulants (for subjects with comorbid ADHD) are allowed to participate in the study. Adult subjects with a positive UDS for cannabinoids are eligible for participation if the use is for medicinal purposes and there is no indication of cannabinoid abuse.

16. Must have a negative alcohol breath test at screening (if applicable) and at baseline (Day -1).

8.2. Exclusion Criteria

8.2.1. Exclusion Criteria for All Subjects

Subjects will be excluded from the study if they:

1. Have an active clinically significant unstable medical condition within 30 days prior to baseline (Day -1).
2. Excessive use of tobacco and/or nicotine-containing products (based on the investigator's assessment) within 30 days of baseline (Day -1).
3. Have a history of substance (drug or alcohol) 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).
4. Are currently pregnant or lactating.
5. Have a known history of neuroleptic malignant syndrome.
6. Have a known history of long QT syndrome or cardiac arrhythmia.
7. Have a screening (if applicable) or baseline (Day -1) triplicate average ECG QT interval corrected for heart rate using Fridericia's formula (QTcF) of >450 msec (adult male subjects and pediatric subjects) or >470 msec (adult female subjects) or the presence of any clinically significant cardiac abnormality.
8. Have a hematologic malignancy or solid tumor diagnosed within 3 years prior to baseline (Day -1), with the exception of localized skin cancer or carcinoma in situ of the cervix.
9. Have received an investigational drug (other than NBI-98854) within 30 days before baseline (Day -1) or plan to use an investigational drug (other than NBI-98854) during the study.
10. Receive any excluded concomitant medication (refer to Section 9.7.1).
11. Have initiated Comprehensive Behavioral Intervention for Tics (CBIT) at baseline (Day -1) or plan to initiate CBIT during the study.
12. Have a significant risk of suicidal or violent behavior. Pediatric subjects with any lifetime suicidal behavior or adult subjects with any suicidal behavior in the past year will be excluded. Any subject with 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 past year based on the "Baseline/Screening version" of the Columbia Suicide Severity Rating Scale (C-SSRS) (assessed at screening or at baseline [Day -1]) will be excluded.
13. Have ingested foods containing poppy seeds within 7 days before baseline (Day -1).
14. Have an allergy, hypersensitivity, or intolerance to tetrabenazine.
15. Have a history of or suspected poor compliance in clinical research studies.

16. **For subjects who require screening only:** Have a clinical laboratory value not within the laboratory's reference range and deemed by the investigator to be clinically significant at screening
17. **For subjects who require screening only:** Have a positive human immunodeficiency virus antibody (HIV-Ab) test result, hepatitis B surface antigen (HBsAg) test result or positive hepatitis C virus antibody (HCV-Ab) test result with a positive HCV polymer chain reaction (PCR) result at screening.

8.2.2. Exclusion Criteria for Pediatric Subjects

In addition to the exclusion criteria for all subjects, the following exclusion criteria apply to pediatric subjects (age 6 to 17 years of age [inclusive]):

18. Have a blood loss ≥250 mL or donated blood within 56 days or donated plasma within 7 days of baseline (Day -1).
19. Have history of severe hepatic impairment or have chronic elevation of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥1.5 times upper limit of normal (ULN).
20. **For subjects who require screening only:** Have AST, ALT, gamma-glutamyl transferase (GGT), total bilirubin, or serum creatinine levels ≥1.5 times the ULN at screening.
21. **For subjects who require screening only:** Have any of the following hematologic abnormalities at screening:
    - Hemoglobin <11.0 g/dL.
    - White blood cell (WBC) count $<4.0 \times 10^3/mm^3$.
    - Platelet count $<100,000/mm^3$.

8.2.3. Exclusion Criteria for Adult Subjects

In addition to the exclusion criteria for all subjects, the following exclusion criteria apply to adult subjects (age 18 to 64 years of age [inclusive]):

22. Have a blood loss ≥550 mL or donated blood within 30 days of baseline (Day -1).
23. Have history of severe hepatic impairment or have chronic elevation of AST or ALT ≥2.5 times ULN.
24. **For subjects who require screening only:** Have any of the following laboratory test abnormalities at screening:
    - Serum creatinine >1.5 times the ULN.
    - AST ≥2.5 times ULN.
    - ALT ≥2.5 times ULN.
    - GGT ≥3.0 times ULN.
    - Total bilirubin >1.5 mg/dL.

25. **For subjects who require screening only:** Have any of the following hematologic abnormalities at screening:
    - Hemoglobin <10.0 g/dL.
    - WBC count <3.0 x $10^3/mm^3$.
    - Platelet count <100,000/mm^3.

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

Subjects will not be randomized in this study.

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 parental or legal guardian informed consent with written and witnessed assent (pediatric subjects), or informed consent (adult subjects) have been obtained. 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[a]	**Screening**[b]	**Baseline**	**Open-Label NBI-98854 Treatment Period**							**Follow-up/ET**
Week[c]	**Day -21 to -2**	**Day -1**	**Day 1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**[d]
Informed consent/assent	X	X[e]								
Inclusion/exclusion criteria	X	X								
Medical history	X	X								
Physical exam (including weight)	X	X[f]		X	X	X	X	X	X	X
Height	X	X[e]								X[g]
Vital signs	X	X[f]		X	X	X	X	X	X	X
12-lead ECG[h]	X	X[f]		X	X	X	X	X	X	X
Pregnancy test[i]	X (s,u)	X (u)		X (u)	X (u)	X (u)	X (u)	X (u)	X (u)	X (u)
Serology (HBsAg, HCV-Ab and HIV-Ab)	X	X[e]								
Clinical laboratory tests[j]	X	X		X	X	X	X	X	X	X
UDS and alcohol breath test[k]	X	X								
Hemoglobin A1c		X				X			X	X
Serum prolactin		X		X		X			X	X
PK blood sample				X	X	X	X	X	X	X
YGTSS (including video recording)		X[f]		X	X	X	X	X	X	X
RTRS		X[f]		X	X	X	X	X	X	X
PUTS		X[f]		X	X	X	X	X	X	X
CGI-Tics-Severity		X[f]		X	X	X	X	X	X	X
CGI-TS and PGIC-TS				X	X	X	X	X	X	X
C-SSRS[l]	X[m]	X[n]		X	X	X	X	X	X	X
ESRS-A		X[f]		X	X	X	X	X	X	X
NBI-98854 dosing at home[o]			X	X	X	X	X	X	X	
Dispense NBI-98854[p]		X		X	X	X	X	X		
NBI-98854 accountability[q]				X	X	X	X	X	X	
AE monitoring	X	X		X	X	X	X	X	X	X
Prior and concomitant medications	X	X		X	X	X	X	X	X	X
Outpatient clinic visits		X		X	X	X	X	X	X	X
Pediatric subjects only PedsQL, CDRS-R, CY-BOCS, ADHD Rating Scale 5: Home Version		X[f]		X	X	X	X	X	X	X
Adults subjects only GTS-QOL, Y-BOCS, SIGH-D-17		X[f]		X	X	X	X	X	X	X

Footnotes and definitions appear on the next page.

ADHD=attention-deficit hyperactivity disorder; AE=adverse event; CDRS-R=Children's Depression Rating Scale-Revised; CGI-Tics-Severity=Clinical Global Impression of Tics-Severity; CGI-TS=Clinical Global Impression of Improvement-Tourette Syndrome; C-SSRS=Columbia Suicide Severity Rating Scale; CY-BOCS=Children's Yale-Brown Obsessive-Compulsive Scale; ECG=electrocardiogram; ESRS-A= Extrapyramidal Symptom Rating Scale-Abbreviated; GTS-QOL=Gilles de la Tourette Syndrome-Quality of Life; HBsAg=hepatitis B surface antigen; HCV-Ab=hepatitis C virus antibody; HIV-Ab=human immunodeficiency virus antibody; PedsQL=Pediatric Quality of Life Inventory; PGIC-TS=Patient Global Impression of Change-Tourette Syndrome; PK=pharmacokinetic; PUTS=Premonitory Urge for Tics Scale; RTRS=Rush Video-based Tic Rating Scale; S=serum; SIGH-D-17=Structured Interview Guide for the Hamilton Depression Rating Scale; U=urine; UDS=urine drug screen; Y-BOCS=Yale-Brown Obsessive-Compulsive Scale; YGTSS=Yale Global Tic Severity Scale.

[a] As much as possible, the study visits should occur at approximately the same time of day in order to standardize the timing of safety, PD, and plasma exposure measurements during each visit.

[b] Screening is not required for subjects who completed NBI-98854-1501 or NBI-98854-1505 within 30 days prior to Day -1.

[c] The study visits after Day -1 will have a visit window of ±6 days.

[d] Final study visit for subjects who complete the study (or early termination).

[e] Not required for subjects who underwent screening.

[f] For subjects completing the final NBI-98854-1501 or NBI-98854-1505 visit on the same day as Day -1, the NBI-98854-1501 or NBI-98854-1505 assessment will be used for Day -1 (not applicable to the PedsQL, ADHD Rating Scale 5: Home Version, or the GTS-QOL).

[g] Measurement of height at follow-up/early termination visit required for pediatric subjects only.

[h] 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.

[i] Pregnancy tests are only required for subjects of childbearing potential. Urine and serum pregnancy tests will be conducted at screening (if applicable). Both pregnancy test results obtained at screening (if applicable) and the urine pregnancy test obtained at baseline (Day -1) will be used to confirm eligibility.

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

[k] For adolescents and adults only. Urine drug screen (UDS) collected at screening (if applicable) and on Day -1 will be analyzed by the central lab; the UDS collected at screening and analyzed by the central lab will be used to confirm eligibility (if applicable). In addition, a UDS kit provided by the central lab will be used at the clinical site to confirm eligibility at screening (if applicable) and on Day -1. A UDS using a kit provided by the central lab may be conducted at the clinical site at any time during the study if the subject is suspected of substance or drug abuse.

[l] The Children's Version will be used for pediatric subjects.

[m] The "Screening/Baseline" version will be administered at screening.

[n] At baseline (Day -1), the "Since Last Visit" version will be administered to subjects who underwent screening, and the "Screening/Baseline" version will be administered to subjects who did not undergo screening.

[o] Study drug will be administered once daily at home at approximately the same time each day under the supervision of the subject's parent/legal guardian (for pediatric subjects) throughout the 24-week treatment period. Day 1 is the first day of dosing, and subjects are not required to come to the study site. Subjects or their parents/legal guardians will record daily the date and time of dosing on the drug packaging form provided. For pediatric subjects only, the study site will call the subject or parent/legal guardian approximately 2 weeks and 6 weeks after starting dosing (ie, at study Weeks 2 and 6) to inquire about any study drug-related issues related to compliance or tolerability.

[p] Subjects will receive a 4-week supply (two kits) of NBI-98854 at Day -1 and will need to return to study site every 4 weeks to obtain a 4-week supply of NBI-98854.

[q] At the end of Weeks 4, 8, 12, 16, 20, and 24 subjects will return all used and unused study drug, and a compliance check will be performed by counting the capsules returned at the visit.

9.2. Pharmacodynamic Assessments

9.2.1. 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 determine if the YGTSS interview program was administered properly. The computer software system for the YGTSS administration, Rater Station[sm] (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 and parent 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 total tic score (TTS) and the Global Tic Severity Score. A copy of the YGTSS is provided in Appendix 17.1.

The YGTSS will be administered at baseline (Day -1) (not required for subjects who have their final NBI-98854-1501 or NBI-98854-1505 study visit on Day -1), during the treatment period (the end of Weeks 4, 8, 12, 16, 20, and 24), and at the follow-up visit (the end of Week 28 or upon early termination).

9.2.2. 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, or draw or color pictures as long as these activities do not block the camera's view of their face, neck and shoulders, arms, and legs. The subject's parent or legal guardian may be present in the room and should sit quietly away from the camera's view. 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 central rater blinded to treatment sequence. A copy of the RTRS is provided in Appendix 17.2.

The RTRS will be administered at baseline (Day -1) (not required for subjects who have their final NBI-98854-1501 or NBI-98854-1505 study visit on Day -1), during the treatment period (the end of Weeks 4, 8, 12, 16, 20, and 24), and at the follow-up visit (the end of Week 28 or upon early termination).

9.2.3. Premonitory Urge for Tics Scale

The 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 at 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. A copy of the PUTS is provided in Appendix 17.3.

The investigator (or designee) will administer the PUTS at baseline (Day -1) (not required for subjects who have their final NBI-98854-1501 or NBI-98854-1505 study visit on Day -1), during the treatment period (the end of Weeks 4, 8, 12, 16, 20, and 24), and at the follow-up visit (the end of Week 28 or upon early termination).

9.2.4. Clinical Global Impression Scales

The CGI-Tics–Severity and CGI-TS scales will be used to rate the subject's overall severity of tics 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 baseline (Day -1) (not required for subjects who have their final NBI-98854-1501 or NBI-98854-1505 study visit on Day -1), during the treatment period (the end of Weeks 4, 8, 12, 16, 20, and 24), and at the follow-up visit (the end of Week 28 or upon early termination). A copy of the CGI-Tics–Severity scale is provided in Appendix 17.4.

The CGI-TS 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 scales will be assessed by the investigator during the treatment period (the end of Weeks 4, 8, 12, 16, 20, and 24), and at the follow-up visit (the end of Week 28 or upon early termination). A copy of the CGI-TS scale is provided in Appendix 17.5.

9.2.5. Patient Global Impression of Change-Tourette Syndrome

Subjects will evaluate the change in their TS symptoms since initiation of study drug dosing by choosing one of seven responses (Very Much Improved; Much Improved; Minimally Improved; Not Changed; Minimally Worse; Much Worse; Very Much Worse).

The Patient Global Impression of Change-Tourette Syndrome (PGIC-TS) will be administered during the treatment period (the end of Weeks 4, 8, 12, 16, 20, and 24), and at the follow-up visit (the end of Week 28 or upon early termination). A copy of the PGIC-TS scale is provided in Appendix 17.6.

9.2.6. Pediatric Quality of Life Inventory (Pediatric Subjects Only)

The Pediatric Quality of Life Inventory (PedsQL) is a valid and reliable instrument that systematically assesses subjects' and parents' perceptions of health-related quality of life (HRQOL) in pediatric subjects with chronic health conditions (Varni et al., 1999). The PedsQL is based on a modular approach to measuring HRQOL and includes a 15-item core measure of global HRQOL and 8 supplemental modules that assess specific symptom or treatment domains.

The PedsQL will be administered at baseline (Day -1), during the treatment period (the end of Weeks 4, 8, 12, 16, 20, and 24), and at the follow-up visit (the end of Week 28 or upon early termination). Three versions of the PedsQL will be used in this study, based on the age of the subject: young child (ages 5-7 years), child (ages 8-12 years), and teen (ages 13-17 years). Copies of each version of the PedsQL are provided in Appendix 17.7.

9.2.7. Gilles de la Tourette Syndrome-Quality of Life Scale (Adult Subjects Only)

The Gilles de la Tourette Syndrome – Quality of Life Scale (GTS-QOL) is a valid, disease-specific, patient-reported scale for the measurement of HRQOL in patients with TS (Cavanna et al., 2008). The GTS-QOL comprises 27 items with 4 subscales (psychological, physical, obsessional, and cognitive). The GTS-QOL will be administered at baseline (Day -1), during the treatment period (the end of Weeks 4, 8, 12, 16, 20, and 24), and at the follow-up visit (the end of Week 28 or upon early termination). A copy of the GTS-QOL is provided in Appendix 17.8.

9.3. Pharmacokinetic Evaluations

Blood samples to evaluate plasma concentrations of NBI-98854, and the metabolite NBI-98782 will be collected during the treatment period (the end of Weeks 4, 8, 12, 16, 20, and 24), and at the follow-up visit (the end of Week 28 or upon early termination).

For each plasma sample, approximately 2 mL of blood will be collected in tubes containing dipotassium ethylenediaminetetraacetic acid (EDTA K_2). 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 2 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.

9.4. Safety Assessments

Concomitant medication use and AEs will be monitored throughout the study as described in Section 9.7.1 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 or followed, including test results obtained at the final study visit or upon 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, CDRS-R, CY-BOCS, Y-BOCS, SIGH-D-17, ADHD Rating Scale, or clinical assessment), the finding will be documented as an AE, and appropriate psychiatric evaluation and intervention will be provided.

9.4.1. Safety Assessments for All Subjects

9.4.1.1. Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will periodically review ongoing clinical safety data to ensure the safety and well-being of the study subjects. The safety data review may result in recommendation for early termination of the study or changes to the protocol and informed consent based on unexpected adverse findings. A DSMB charter will describe the responsibilities, timing of meetings, and data review procedures for the members to follow.

9.4.1.2. Medical history

A medical history will be taken at screening (if applicable) and at baseline (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.

9.4.1.3. 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 (if applicable), baseline (Day -1) (not required for subjects who have their final NBI-98854-1501 or NBI-98854-1505 study visit on Day -1), during the treatment period (the end of Weeks 4, 8, 12, 16, 20, and 24), and at the follow-up visit (the end of Week 28 or upon early termination). Height will be measured at screening (if applicable), baseline (Day -1; not required for subjects who underwent screening) and at the end of Week 28 (or upon early termination) (height measurement at the end of Week 28 or upon early termination is not required for adult subjects) only. Height and weight will be measured with subjects not wearing shoes.

9.4.1.4. 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 (if applicable), baseline (Day -1) (not required for subjects who have their final NBI-98854-1501 or NBI-98854-1505 study visit on Day -1), during the treatment period (the end of Weeks 4, 8, 12, 16, 20, and 24), and at the follow-up visit (the end of Week 28 or upon early termination). Vital sign measurements will be obtained before any scheduled blood sample collection.

9.4.1.5. 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 HR, PR interval, QRS duration, QT interval, and QTcF (machine readings or calculated). Additionally, the occurrence of de- and re-polarization and rhythm disorders or other abnormalities will be assessed. Based on the review of these parameters, the investigator or designee will note if the ECG is Normal, Abnormal not Clinically Significant, or Abnormal Clinically Significant. If the ECG is Abnormal Clinically Significant, the investigator or designee will provide a description of the abnormality recorded on the AE eCRF.

The 12-lead ECG recordings will be conducted at screening (if applicable), baseline (Day -1) (not required for subjects who have their final NBI-98854-1501 or NBI-98854-1505 study visit on Day -1), during the treatment period (the end of Weeks 4, 8, 12, 16, 20, and 24), and at the follow-up visit (the end of Week 28 or upon early termination).

9.4.1.6. 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 laboratory tests. Laboratory samples will be collected in the following approximate amounts: Children (6 to 11 years of age) – 3 mL for hematology and 2.5 mL for serum chemistry; adolescents and adults (12 to 64 years of age) – 4 mL for hematology and 5 mL for serum chemistry (includes serum pregnancy tests for female subjects of childbearing potential).

Clinical safety laboratory assessments will be performed at screening (if applicable) baseline (Day -1), during the treatment period (the end of Weeks 4, 8, 12, 16, 20, and 24), and at the follow-up visit (the end of Week 28 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 hemoglobin concentration (MCHC), mean corpuscular volume (MCV), 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, gamma-glutamyl transferase (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:

Hemoglobin A1c: Blood samples for hemoglobin A1c will be collected at baseline (Day -1), at the end of weeks 12, 24, and at the follow-up visit (the end of Week 28 or upon early termination). Approximately 2 mL in EDTA K_2 will be collected in all subjects.

Serum Prolactin: Blood samples to determine serum prolactin concentration will be collected at baseline (Day -1), at the end of Weeks 4, 12, and 24, and at the follow-up visit (the end of Week 28 or upon early termination). Approximately 2.5 mL (children, 6 to 11 years of age) or 5 mL (adolescents and adults, 12 to 64 years of age) 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 human immunodeficiency virus antibody (HIV-Ab), hepatitis B surface antigen (HBsAg), and hepatitis C virus antibody (HCV-Ab) testing at screening (if applicable) or at baseline (Day -1). 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: 9 mL (children, 6 to 11 years of age) or 10 mL (adolescents and adults, 12 to 64 years of age).

Urine Drug Screen and Alcohol Breathalyzer Test: The UDS 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 UDS and alcohol breathalyzer test will be performed at screening (if applicable) and at baseline (Day -1). The UDS and alcohol breathalyzer test will be performed only in adolescent and adults subjects (12 to 64 years of age). A UDS using a kit provided by the central lab 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: Pregnancy tests will be conducted for female subjects of childbearing potential only; subjects will be required to comply with protocol-required pregnancy testing from the time of menarche. A serum pregnancy test and a urine pregnancy test will be conducted at screening (if applicable); urine pregnancy tests will be conducted at screening (if applicable), baseline (Day -1), during the treatment period (the end of Weeks 4, 8, 12, 16, 20, and 24), and at the follow-up visit (the end of Week 28 or upon early termination).

9.4.1.7. Columbia-Suicide Severity Rating Scale

The C-SSRS is a validated instrument to prospectively assess suicidal ideation and behavior (http://www.cssrs.columbia.edu). At the screening visit, or baseline visit for subjects that do not require a screening visit, the Baseline/Screening version will be administered (Children's Baseline/Screening version for pediatric subjects). For all subsequent visits (except for unscheduled visits), the Since Last Visit version will be administered (Children's Since Last Visit version for pediatric subjects). All versions of the C-SSRS include a series of screening questions related to suicidal ideation and suicidal behavior. Subject responses of "yes" to 1 or more screening questions will prompt additional questions that evaluate frequency and intensity of suicidal ideation and/or behavior. Copies of each version of the C-SSRS are provided in Appendix 17.9.

The C-SSRS will be administered and scored by the investigator or qualified study site personnel at screening (if applicable), baseline (Day -1), during the treatment period (the end of

Weeks 4, 8, 12, 16, 20, and 24), and at the follow-up visit (the end of Week 28 or upon early termination).

9.4.1.8. Extrapyramidal Symptom Rating Scale-Abbreviated

The ESRS-A is a psychometrically valid instrument that assesses four types of movement disorders: Parkinsonism, akathisia, dystonia, and TD (Chouinard and Margolese, 2005). The investigator (or designee) will administer the ESRS-A at baseline (Day -1) (not required to be repeated for subjects who had this assessment conducted at their final NBI-98854-1501 or NBI-98854-1505 study visit), during the treatment period (the end of Weeks 4, 8, 12, 16, 20, 24), and at the follow-up visit (the end of Week 28 or upon early termination). A copy of the ESRS-A is provided in Appendix 17.15.

9.4.1.9. 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 at screening (if applicable), baseline (Day -1), the treatment periods, and the final visit (or upon early termination).

Table 2: Estimated Total Blood Sample Volume

Parameter	Number of Samples Required	Approximate Volume (mL)	Approximate Total Volume (mL)
Children (6 to 11 years of age)			
Serum chemistry[a]	9[b]	2.5	22.5
Hematology	9[b]	3	27
Hemoglobin A1c	4	2	8
Serology	1	9	9
Serum prolactin	5	2.5	12.5
Pharmacokinetics	7	2[c]	14
Approximate Maximum Total Blood Sample Volume per Subject (mL):			**93**
Adolescents (12 to 17 years of age)			
Serum chemistry[a]	9[b]	5	45
Hematology	9[b]	4	36
Hemoglobin A1c	4	2	8
Serology	1	10	10
Serum prolactin	5	5	25
Pharmacokinetics	7	2[c]	14
Approximate Maximum Total Blood Sample Volume per Subject (mL):			**138**
Adults (18 to 64 years of age)			
Serum chemistry[a]	9[b]	5	45
Hematology	9[b]	4	36
Hemoglobin A1c	4	2	8
Serology	1	10	10
Serum prolactin	5	5	25
Pharmacokinetics	7	2[c]	14
Approximate Maximum Total Blood Sample Volume per Subject (mL):			**138**

[a] Includes pregnancy test at screening (if applicable) for female subjects who are of childbearing potential.
[b] Subjects who do not require screening will only require 8 samples.
[c] Includes 0.5 mL of discard volume per sample.

9.4.2. Safety Assessments for Pediatric Subjects Only

9.4.2.1. Children's Depression Rating Scale, Revised

The CDRS-R is a 17-item, semi-structured interview to determine the severity of depression in children. The investigator (or designee) will administer the CDRS-R at baseline (Day -1) (not required for subjects who have their final NBI-98854-1501 study visit on Day -1), during the treatment period (the end of Weeks 4, 8, 12, 16, 20, and 24), and at the follow-up visit (the end of Week 28 or upon early termination). A copy of the CDRS-R is provided in Appendix 17.10.

9.4.2.2. Children's Yale-Brown Obsessive-Compulsive Scale

The CY-BOCS is a semistructured interview designed to rate the severity of obsessive and compulsive symptoms in children. The investigator (or designee) will administer the CY-BOCS at baseline (Day -1) (not required for subjects who have their final NBI-98854-1501 study visit on Day -1), during the treatment period (the end of Weeks 4, 8, 12, 16, 20, and 24), and at the

follow-up visit (the end of Week 28 or upon early termination). A copy of the CY-BOCS is provided in Appendix 17.11.

9.4.2.3. Attention-Deficit Hyperactivity Disorder Rating Scale 5: Home Version

The ADHD Rating Scale 5: Home Version will be used to determine the frequency and severity of ADHD symptoms and impairments over the past month. The scale comes in 2 versions: child (ages 5-10 years) and adolescent (ages 11-17 years). Both versions consist of 2 symptom subscales, Inattention (9 items) and Hyperactivity–Impulsivity (9 items), as well as a Total Scale (18 items). In addition, 6 domains of impairment that are common among children with ADHD are assessed: relationships with significant others (family members for the home version and teachers for the school version), peer relationships, academic functioning, behavioral functioning, homework performance, and self-esteem.

It will be completed independently by the subject's parent or guardian at baseline (Day -1), during the treatment period (the end of Weeks 4, 8, 12, 16, 20, and 24), and at the follow-up visit (the end of Week 28 or upon early termination). Copies of both versions of the ADHD Rating Scale 5: Home Version are provided in Appendix 17.12.

9.4.3. Safety Assessments for Adult Subjects Only

9.4.3.1. 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 baseline (Day -1) (not required for subjects who have their final NBI-98854-1505 study visit on Day -1), during the treatment period (the end of Weeks 4, 8, 12, 16, 20, and 24), and at the follow-up visit (the end of Week 28 or upon early termination). A copy of the Y-BOCS is provided in Appendix 17.13.

9.4.3.2. 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 baseline (Day -1) (not required for subjects who have their final NBI-98854-1505 study visit on Day -1), during the treatment period (the end of Weeks 4, 8, 12, 16, 20, and 24), and at the follow-up visit (the end of Week 28 or upon early termination). A copy of the SIGH-D-17 is provided in Appendix 17.14.

9.5. Specific Study Information

Study visits during the treatment period at the end of weeks 4, 8, 12, 16, 20, 24, and 28 (or upon early termination) will have a visit window of ±6 days.

9.5.1. Screening (Days -21 to -2)

Subjects who have their final NBI-98854-1501 or NBI-98854-1505 visit >30 days prior to anticipated baseline (Day -1) must undergo screening. These subjects will be screened to determine eligibility within 20 days (Days -21 to -2) before baseline (Day -1).

During screening, the following will be performed:

- Obtain informed consent/assent.
- Assess inclusion/exclusion criteria.
- Collect medical history.
- Perform a physical examination (including weight).
- Measure height
- Collect vital signs, including orthostatic systolic and diastolic blood pressures, orthostatic pulse rate, respiratory rate, and oral body temperature.
- Perform 12-lead ECG in triplicate (1-3 minutes apart).
- Perform a serum pregnancy test (human chorionic gonadotropin [β-hCG]) and a urine pregnancy test 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 UDS (both only in adolescent and adult subjects).
- Administer the C-SSRS (Children's Screening/Baseline version for pediatric subjects and Screening/Baseline version for adult subjects).
- Record prior medications.
- Monitor for AEs

9.5.2. Baseline (Day -1)

Subjects who have their final NBI-98854-1501 or NBI-98854-1505 visit on the same day as Day -1 for the current study can have certain PD and safety assessments to be used for both the previous study and the current study. The PD assessments that can apply to both the previous study and the current study include the YGTSS, RTRS, PUTS, and CGI-Tics-Severity. The safety assessment results that can apply to both the previous study and the current study include physical examinations (including weight), vital signs, ECGs, ESRS-A, CY-BOCS (pediatric subjects only), CDRS-R (pediatric subjects only), Y-BOCS (adult subjects only), and the SIGH-D-17 (adult subjects only).

The following evaluations and tasks will be performed at baseline (Day -1):

- Obtain informed consent/assent (not required for subjects who underwent screening).
- Assess inclusion/exclusion criteria.
- Collect medical history.
- Perform a physical examination (including weight).

- Measure height (not required for subjects who underwent screening).
- Collect vital signs, including orthostatic systolic and diastolic blood pressures, orthostatic pulse rate, respiratory rate, and oral body temperature.
- Perform 12-lead ECG in triplicate (1-3 minutes apart).
- Perform a urine pregnancy test only for female subjects of childbearing potential.
- Collect blood sample for serology testing (not required for subjects who underwent screening).
- Collect blood sample for hematology and clinical chemistry.
- Collect urine sample for urinalysis.
- Perform alcohol breathalyzer test and UDS (both only in adolescent and adult subjects).
- Collect blood sample for hemoglobin A1c.
- Collect blood sample for serum prolactin.
- Administer the YGTSS, including video recording.
- Video record subjects for the RTRS.
- Give the PUTS to the subject or parent/legal guardian to complete.
- Administer the CGI-Tics-Severity scale.
- Administer the C-SSRS (Children's version for pediatric subjects; the "Since Last Visit" version will be administered to subjects who underwent screening, and the "Screening/Baseline" version will be administered to subjects who did not undergo screening).
- Administer the ESRS-A.
- Administer the PedsQL, CDRS-R, and CY-BOCS (pediatric subjects only).
- Give the ADHD Rating Scale 5: Home Version to the subject or parent/legal guardian to complete (pediatric subjects only).
- Administer the GTS-QOL, Y-BOCS, and SIGH-D-17 (adult subjects only).
- Record prior medications.

After completion of these assessments, if the subject is eligible for the study the clinical site will access the Interactive Web Response System (IWRS) to obtain an identification number for a kit containing a 4-week supply of NBI-98854 to be dispensed to the subject. At this point, the subject will be considered enrolled in the study.

Enrolled subjects will:

- Be monitored for AEs.
- Be instructed to take NBI-98854 at home at approximately the same time each day (in the presence of their caregiver, if applicable) beginning the following day (Day 1). NBI-98854 must be swallowed with at least 4 oz. of water.
- Instruct subjects or parents/legal guardians to record the date and time of each dose on the labels provided on the study drug packaging form.

- Be instructed to continue using contraception (other than subjects not required to use contraception; see inclusion criterion #9 in Section 8.1).
- Be instructed to return to the site for the Week 4 visit. The following should be taken into account for scheduling purposes: As much as possible, the Weeks 4, 8, 12, 16, 20, 24 and the follow-up visit should occur at approximately the same time as the baseline (Day -1) visit in order to standardize the time of day for the assessment of safety, PD, and plasma exposure throughout the study period.
- Be instructed to contact the clinical site immediately without waiting for the next scheduled visit to report AEs or before starting any new medication.
- Be instructed to return all unused NBI-98854 and packaging at the next scheduled visit.

9.5.3. Treatment Period

9.5.3.1. Day 1

Beginning on Day 1, subjects will take NBI-98854 at home at approximately the same time each day (in the presence of their caregiver, if applicable). NBI-98854 must be swallowed with at least 4 oz. of water.

9.5.3.2. Weeks 2 and 6

For pediatric subjects only, the study site will call the subject or parent/legal guardian approximately 2 weeks and 6 weeks after starting dosing (ie, at study Weeks 2 and 6) to inquire about any study drug-related issues related to compliance or tolerability.

9.5.3.3. Weeks 4, 8, 12, 16, 20, and 24 (±6 days for each visit)

Subjects and parents/legal guardians (if applicable) will report to the study site at the end of Weeks 4, 8, 12, 16, 20, and 24.

At the end of Weeks 4, 8, 12, 16, 20, and 24 the following study evaluations and procedures will be performed at the study site:

- Perform a physical examination including weight.
- Collect vital signs, including orthostatic systolic and diastolic blood pressures, orthostatic pulse rate, respiratory rate, and oral 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 hemoglobin A1c (Weeks 12 and 24 only).
- Collect blood sample for serum prolactin (Weeks 4, 12, and 24 only).
- Collect PK blood sample for NBI-98854 and metabolite concentrations.
- Administer the YGTSS, including video recording.
- Video record subjects for the RTRS.

- Give the PUTS to the subject or parent/legal guardian to complete.
- Administer the CGI-Tics-Severity scale.
- Administer the CGI-TS scale.
- Give the PGIC-TS scale to the subject or parent/legal guardian to complete.
- Administer the C-SSRS (Children's Since Last Visit version for pediatric subjects and Since Last Visit version for adults).
- Administer the ESRS-A.
- Administer the PedsQL, CDRS-R, and CY-BOCS (pediatric subjects only).
- Give the ADHD Rating Scale 5: Home Version to the subject or parent/legal guardian to complete (pediatric subjects only).
- Administer the GTS-QOL, Y-BOCS, and SIGH-D-17 (adult subjects only).
- Dispense a 4-week supply of study drug (Weeks 4, 8, 12, 16, and 20 only).
- Instruct subjects or parents/legal guardians to record the date and time of each dose on the labels provided on the study drug packaging form (Weeks 4, 8, 12, 16, and 20 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 site:

- Instruct subjects to continue using contraception (other than subjects not required to use contraception; see inclusion criterion #9 in Section 8.1).
- Instruct subjects and parents/legal guardians (if applicable) to notify the investigator by telephone if they experience any AEs and before taking any new concomitant medications.

Dose Titration Assessment

At the end of Week 4 of the treatment period, the investigator may escalate a child's dose to 20 mg, an adolescent's dose to 40 mg, an adult's dose to 80 mg, or continue with the subject's current dose for the remainder of the treatment period. A dose escalation will be allowed at the end of Week 4 if (1) the investigator or designee's assessment of the CGI-TS is "minimally improved", "not changed", "minimally worse", "much worse", or "very much worse", and (2) the safety and tolerability of the current dose is acceptable as determined by a physician. The subject will then continue at the 20 mg dose (for children), 40 mg dose (for adolescents), or 80 mg dose (for adults) until the end of the treatment period (ie, the end of Week 24).

At any time after dose escalation, the investigator may decrease the dose to 10 mg for a child, 20 mg for an adolescent, or 40 mg for an adult if the subject is unable to tolerate the dose increase. The subject will then continue at the 10 mg, 20 mg, or 40 mg dose until the end of the treatment period (end of Week 24). Subjects who are unable to tolerate the starting dose of 10 mg for children, 20 mg for adolescents, or 40 mg for adults, or the resumption of the 10 mg, 20 mg, or 40 mg dose following a tolerability issue after the dose escalation at Week 4, will be discontinued from the study.

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

9.5.4. Follow-Up: Week 28 (±6 days) (or Early Termination)

At the follow-up visit (the end of Week 28 or upon early termination) the following procedures will be performed at the study site:

- Perform a physical examination including height and weight (height is measured in pediatric subjects only).
- Collect vital signs, including orthostatic systolic and diastolic blood pressures, orthostatic pulse rate, respiratory rate, and oral 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 hemoglobin A1c.
- 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.
- Give the PUTS to the subject or parent/legal guardian to complete.
- Administer the CGI-Tics–Severity scale.
- Administer the CGI-TS scale.
- Give the PGIC-TS scale to the subject or parent/legal guardian to complete.
- Administer the C-SSRS (Children's Since Last Visit version for pediatric subjects and Since Last Visit version for adults).
- Administer the ESRS-A.
- Administer the PedsQL, CDRS-R, and CY-BOCS (pediatric subjects only).
- Give the ADHD Rating Scale 5: Home Version to the subject or parent/legal guardian to complete (pediatric subjects only).
- Administer the GTS-QOL, Y-BOCS, and SIGH-D-17 (adult subjects only).
- AE monitoring.
- Record concomitant medications.

9.6. Study Duration

The expected duration of study participation for each subject is up to 31 weeks, including a 3-week screening period, a 24-week treatment period, and a 4-week follow-up period.

9.7. Prohibitions and Restrictions

9.7.1. Prior and Concomitant Medications

All prescription and over-the-counter medications, including dietary and herbal supplements, taken by subjects during the 30 days before baseline (Day -1) and during the study will be entered on the Prior and Concomitant Medications eCRF. Any additions, deletions, or changes in the dose of these medications will be entered on the eCRF with indication, dose, route, and dates of drug administration.

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

- Antiemetics: Metoclopramide, prochlorperazine, and promethazine are prohibited.
- Botulinum toxin: Botulinum toxin injections for the treatment of TS symptoms are prohibited starting 90 days prior to baseline (Day -1) 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.
- VMAT2 inhibitors: VMAT2 inhibitor medications (eg, tetrabenazine, reserpine) are prohibited, except for study drug.
- 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.

9.7.2. 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 baseline (Day -1) until the follow-up visit. Foods containing poppy seeds are prohibited from 7 days before baseline (Day -1) until the follow-up visit. For adult subjects only, moderate alcohol consumption (1 to 2 drinks per day or 7 to 14 drinks per week) is allowed from 48 hours before baseline (Day -1) until the follow-up visit.

9.7.3. 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 baseline [Day -1] to the follow-up visit or upon 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. Adult 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 at baseline (Day -1) or plan to initiate CBIT during the study.

9.8. 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 must withdraw the subject from the study if the subject experiences any of the following:

- If the type, frequency, or severity of any AE become unacceptable/intolerable.
- If the subject is unable to tolerate the starting dose or resumption of the previous dose.
- QTcF value >500 msec (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 ≥2.5 times ULN) or ECG abnormality.
- Requires a medication that is prohibited by the protocol (refer to Section 9.7.1).
- 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 9.5.4).

9.8.1. Handling of Withdrawals

If a subject prematurely withdraws from the study, either at his/her request, at the request of the parent or legal guardian, or at the investigator's discretion, the investigator will record the reason for withdrawal on the relevant eCRF. All subjects who withdraw from the study prematurely will be asked to have all early termination assessments performed within 4 weeks.

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.

9.8.2. Sponsor's Termination of Study

NBI reserves the right to discontinue the study at any time for clinical or administrative reasons.

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

10. STUDY DRUG

10.1. Study Drug Supplies

NBI or its designee will provide the study sites with subject-specific, study drug kits sufficient for the completion of the treatment period of the study.

NBI-98854 will be supplied as capsules containing 10, 20, or 40 mg of NBI-98854 (free base). The NBI-98854 80 mg dose will be administered as two 40 mg capsules. The NBI-98854 10, 20, and 40 mg capsules are a white, opaque, HPMC No. 3 size capsule containing 10, 20, and 40 mg, respectively of NBI-98854 (dose is of the free base) and is formulated using Capsugel shells.

10.2. Study Drug Storage

NBI-98854 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 GCP rules. The study drugs will be sent to authorized staff at the study site. The authorized study staff member must confirm receipt of the study drug to NBI or its designee 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. At each visit that NBI-98854 is dispensed (see Table 1), subjects will receive 2 blistercards. The blistercards will contain capsules of NBI-98854 10 mg, 20 mg, or 40 mg.

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

10.4. Blinding

Not applicable as this is an open-label study.

10.5. Study Drug Administration

On Day -1, eligible children 6 to 11 years of age will receive a supply of NBI-98854 10 mg, eligible adolescents 12 to 17 years of age will receive a supply of NBI-98854 20 mg, and eligible adults 18 to 64 years of age will receive a supply of NBI-98854 40 mg, for the first 4 weeks of the treatment period. Beginning on Day 1, study drug will be administered once daily at home at approximately the same time each day under the supervision of the subject's parent/legal guardian and the capsules must be swallowed with at least 4 oz. of water every day throughout the 24-week treatment period.

At the end of Week 4 of the treatment period, the investigator may escalate a child's dose to 20 mg, an adolescent's dose to 40 mg, an adult's dose to 80 mg, or continue with the subject's current dose for the remainder of the treatment period. A dose escalation will be allowed at the end of Week 4 if (1) the investigator or designee's assessment of the CGI-TS is "minimally improved", "not changed", "minimally worse", "much worse", or "very much worse", and (2) the safety and tolerability of the current dose is acceptable as determined by a physician. The subject will then continue at the 20 mg dose (for children), 40 mg dose (for adolescents), or 80 mg dose (for adults) until the end of the treatment period (ie, the end of Week 24).

At any time after dose escalation, the investigator may decrease the dose to 10 mg for a child, 20 mg for an adolescent, or 40 mg for an adult, if the subject is unable to tolerate the dose increase. The subject will then continue at the 10 mg, 20 mg, or 40 mg dose until the end of the treatment period (end of Week 24). Subjects who are unable to tolerate the starting dose of 10 mg for children, 20 mg for adolescents, 40 mg for adults, or the resumption of the 10 mg, 20 mg, or 40 mg dose following a tolerability issue after the dose escalation at Week 4, will be discontinued from the study.

If a subject forgets or is unable to take study drug within a few hours of the normal dosing time, the subject should skip his or her daily dose and resume normal dosing the following day.

If a subject changes dosing time (eg, changes from morning to evening dosing), the subject should dose at the new time the following day. Subjects or their parents/legal guardians will record the date and time of study drug dosing each day on the labels provided on the study drug packaging form.

10.6. Drug Compliance and Accountability

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

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 ICF/assent is signed until the subject's final study day (Week 28 or upon 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 study drug administration, unless it unexpectedly progresses, or increases in severity following study 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
Mild	An AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	An AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
Severe	An AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

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 AE (Title 21 CFR 312.32 [a]).

Table 4: Relationship of Adverse Events to Study Drug

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

11.4. Recording Adverse Events

For enrolled subjects, each AE will be listed as a separate entry on an AE eCRF. 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:

- SAE, 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 final visit or upon 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 ICF/assent is signed 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 AE. Life threatening means that the subject was, in the view of the investigator or sponsor, at immediate risk of death from the reaction as it occurred. It does not mean that hypothetically the event might have caused death if it occurred in a more serious form.
- Inpatient hospitalization or prolongation of existing hospitalization. Hospitalization for elective treatment or a preexisting condition that did not worsen during the clinical investigation is not considered an AE. Hospitalization or nursing home admission for the purpose of caregiver respite is not considered an AE. Complications that occur during hospitalization are AEs, and if a complication prolongs hospitalization, the event is considered serious. Treatment in a hospital emergency room is not a hospitalization.
- A persistent or significant incapacity or substantial disruption of a person's ability to conduct normal life functions.
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life threatening, or require hospitalization. These events may be considered serious when, based on appropriate medical judgment, they may jeopardize the health of the subject and may require medical or surgical intervention to prevent one of the outcomes listed. Any other event thought by the investigator to be serious should also be reported, following the reporting requirements detailed in this section. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

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 NBI Medical Monitor (and the IRB, if necessary) immediately (within 24 hours) of the SAE and the outcome of the SAE.

If within the time of informed consent until 30 days after the last dose of study drug or final study visit (whichever is longer in duration), an investigator becomes aware of an SAE, then the event must be documented and reported as described in Section 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: [redacted]
CDS facsimile:
CDS e-mail:
NBI Medical Monitor: **Telephone:** [redacted]
Cell phone:

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 contraception (other than subjects not required to use contraception; see inclusion criterion #9 in Section 8.1) until 30 days after the last dose of study drug for female subjects and 90 days after the last dose of study drug for male subjects. If at any time between the time the subject signs the ICF/assent and the last study visit a subject believes she is pregnant, the subject will be instructed to stop taking the study medication and return to the study site within 24 hours and undergo a serum pregnancy test to confirm pregnancy.

All confirmed pregnancies, in subjects who received study drug, must be immediately reported to NBI (refer to Section 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 NBI portal of the EDC system for the duration of the study through a password-protected method of internet access. Such access will be removed from 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 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. Descriptive statistics will be presented for each age group (note that additional summaries by treatment as well as pooled data summaries may be specified in the detailed statistical analysis plan [SAP]).

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

13.1. Analysis Sets

A single analysis set, the safety analysis set, will be defined for this study. The safety analysis set will include all subjects who take at least one dose of study drug and have any postdosing safety data.

13.2. Sample Size

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

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 enrolled, who received at least 1 dose of study drug, who completed the 24-week treatment period, and who completed the study. The number of subjects who did not complete the study will also be summarized, 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 (data obtained from NBI-98854-1501 or

NBI-98854-1505 study results), age at TS diagnosis, and baseline values for the TTS) will be summarized with descriptive statistics. Medical history will also be summarized.

13.6. Study Drug Dosing and Compliance

The number and percentage of subjects who are dosing compliant (>80% of doses taken) during the treatment period will be summarized by visit. Cumulative dosing compliance through Week 24 will be summarized as well.

13.7. Pharmacokinetic Data

The plasma concentrations of NBI-98854 and the metabolite NBI-98782 will be summarized with descriptive statistics by visit. Concentrations below the lower limit of quantification will be set equal to zero for all plasma concentration summaries.

13.8. Pharmacodynamic Data

The PD measures in this study are:

- All subjects: YGTSS, RTRS, PUTS, CGI-Tics-Severity, CGI-TS, and PGIC-TS.
- Pediatric subjects only: PedsQL.
- Adult subjects only: GTS-QOL.

For each PD measure, descriptive statistics will be presented for each visit and for the changes from baseline (Day -1) to each postbaseline visit.

13.9. Safety Data

TEAEs, 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, vital signs, ECG, ESRS-A, C-SSRS, CY-BOCS, CDRS-R, ADHD Rating Scale 5: Home Version, 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 Food and Drug Administration (FDA), and the ICH Guidelines for GCP. All clinical work conducted under this protocol is subject to GCP rules. This includes an inspection by NBI or its representative, health authority, or IRB representatives at any time. The investigator must agree to the inspection of study related records by health authority representatives and/or NBI or its designee.

14.2. Institutional Review Board

The final approved protocol, the ICF, and assent document 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 the protocol, consent form, and assent form.
- Copy of the IRB approved written ICF and assent to be used.
- Laboratory documents (certifications/accreditations, normal ranges) if not provided by a central laboratory.

14.5. Informed Consent

For pediatric subjects, all parents or legal guardians will provide informed consent with signed and witnessed pediatric assent before the performance of any study related procedures.

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

Each subject's chart will include the signed ICF with signed and witnessed pediatric assent for study participation (if applicable). When the study treatment is completed and the eCRF has been monitored, the ICF and signed and witnessed pediatric assent will be kept in the investigator's central study file. Regulatory authorities may check the existence of the signed ICF and the signed and witnessed pediatric assent in this central study folder.

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, and according to national law. Quality assurance audits may be performed at the discretion of NBI.

14.8. Record Retention

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

14.9. Confidentiality

NBI 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

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.

16. REFERENCES

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. 1994.

Baxter LR, Guze BH. Neuroimaging. In: Kurlan, R. (Ed), Handbook of Tourette syndrome and related tic and behavioral disorders. Rochester: Marcel Decker Inc.; 1993.

Braun AR, Stoetter B, Randolph C, Hsiao JK, Vladar K, Gernert J, et al. The functional neuroanatomy of Tourette's syndrome: an FDG-PET study. I. Regional changes in cerebral glucose metabolism differentiating patients and controls. Neuropsychopharmacology. 1993 Dec;9(4):277-91.

Cavanna AE, Schrag A, Morley D, Orth M, Robertson MM, Joyce E, et al. The Gilles de la Tourette syndrome-quality of life scale (GTS-QOL): development and validation. Neurology. 2008 Oct;71(18):1410-6.

Cavanna AE, Nani A. Tourette syndrome and consciousness of action. Tremor Other Hyperkinet Mov (NY). 2013 Sep;3.

Chen JJ, Ondo WG, Dashtipour K, Swope DM. Tetrabenazine for the treatment of hyperkinetic movement disorders: a review of the literature. Clin Therapeutics. 2012;34:1487-1504.

Chouinard G and Margolese HC. Manual for the Extrapyramidal Symptom Rating Scale (ESRS). Schizophr Res. 2005 Jul 15;76(2-3):247-65.

Felling RJ, Singer HS. Neurobiology of Tourette syndrome: current status and need for further investigation. J Neurosci. 2011 Aug;31(35):12387-95.

Goetz CG, Pappert EJ, Louis ED, Raman R, Leurgans S. Advantages of a modified scoring method for the Rush Video-based Tic Rating Scale. Mov Disord. 1999 May;14(3):502-6.

Leckman JF, Riddle MA, Hardin MT, Ort SI, Swartz KL, Stevenson J, et al. The Yale Global Tic Severity Scale: initial testing of a clinician-rated scale of tic severity. J Am Acad Child Adolesc Psychiatry. 1989 Jul;28(4):566-73.

Pourfar M, Feigin A, Tang CC, Carbon-Correll M, Bussa M, Budman C, et al. Abnormal metabolic brain networks in Tourette syndrome. Neurology. 2011 Mar;76(11):944-52.

Roessner V, Schoenefeld K, Buse J, Bender S, Ehrlich S, Münchau A. Pharmacological treatment of tic disorders and Tourette Syndrome. Neuropharmacology. 2013 May;68:143-9.

Shprecher D, Kurlan R. The management of tics. Mov Disord. 2009 Jan;24(1):15-24.

Varni JW, Seid M, Rode CA. The PedsQL: measurement model for the pediatric quality of life inventory. Med Care. 1999 Feb;37(2):126-39.

Woods DW, Piacentini J, Himle MB, Chang S. Premonitory Urge for Tics Scale (PUTS): initial psychometric results and examination of the premonitory urge phenomenon in youths with Tic disorders. J Dev Behav Pediatr. 2005 Dec;26(6):397-403.