CLINICAL STUDY PROTOCOL

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A Phase 2b, Randomized, Double-Blind, Placebo-Controlled, Dose Optimization Study to Assess the Safety, Tolerability, and Efficacy of NBI-98854 for the Treatment of Pediatric Subjects with Tourette Syndrome

Study No.: NBI-98854-TS2003

Development Phase: Phase 2b

Sponsor: Neurocrine Biosciences, Inc.
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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) (Harmonised)
- United States (US) Code of Federal Regulations (CFR); US Food and Drug Administration (FDA); Health Canada.

CLINICAL STUDY TITLE:

A Phase 2b, Randomized, Double-Blind, Placebo-Controlled, Dose Optimization Study to Assess the Safety, Tolerability, and Efficacy of NBI-98854 for the Treatment of Pediatric Subjects with Tourette Syndrome

PROTOCOL No.: NBI-98854-TS2003

As Agreed:

_____ _____

Principal Investigator Signature Date

PRINCIPAL INVESTIGATOR:

_____

(Print Principal Investigator Name)

SITE:

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7/31/2018
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2. SYNOPSIS

Protocol Title:

A Phase 2b, Randomized, Double-Blind, Placebo-Controlled, Dose Optimization Study to Assess the Safety, Tolerability, and Efficacy of NBI-98854 for the Treatment of Pediatric Subjects with Tourette Syndrome

Study Centers: Approximately 55 study centers in North America.

Objectives:

Primary:

- To evaluate the efficacy of NBI-98854, titrated to the subject's optimal dose in the range of 20 mg to 60 mg for subjects <50 kg and 40 mg to 80 mg for subjects ≥50 kg, administered once daily (qd) for the treatment of Tourette syndrome (TS).

Secondary:

- To evaluate the safety and tolerability of NBI-98854, titrated to the subject's optimal dose in the range of 20 mg to 60 mg for subjects <50 kg and 40 mg to 80 mg for subjects ≥50 kg, administered once daily.
- To evaluate plasma exposure measures of NBI-98854 and its active metabolite, NBI-98782, following titrated doses of NBI-98854 from 20 mg to 60 mg for subjects <50 kg and 40 mg to 80 mg for subjects ≥50 kg.

Methodology: This is a Phase 2b, randomized, double-blind, placebo-controlled, dose-optimization study to evaluate the efficacy, safety, and tolerability of NBI-98854 titrated to the subject's optimal dose in the range of 20 mg to 60 mg for subjects <50 kg and 40 mg to 80 mg for subjects ≥50 kg compared to placebo, administered qd for a total of 12 weeks of treatment in pediatric subjects with TS. Approximately 120 male and female pediatric subjects, 6 to 17 years of age, with a Diagnostic and Statistical Manual of Mental Disorders, 4th or 5th Editions (DSM-IV or -V) diagnosis of TS will participate. There will be an approximately equal distribution of subjects in each weight group, <50 kg and ≥50 kg, enrolled into the study and subjects will be stratified based on their weight. Eligible subjects will be randomized in a 1:1 ratio to NBI-98854 or placebo treatment as depicted in the following table:

Weight Group Assigned Treatment	**Number of Subjects (approximate)**
Subjects <50 kg at baseline	
Placebo	30
NBI-98854 (20 to 60 mg)	30
Subjects ≥50 kg at baseline	
Placebo	30
NBI-98854 (40 to 80 mg)	30

For subjects randomized to active treatment, the starting dose will be NBI-98854 20 mg for subjects <50 kg at baseline and NBI-98854 40 mg for subjects ≥50 kg at baseline, which may be escalated in increments of 20 mg every 2 weeks to a maximum of 60 mg for subjects <50 kg and 80 mg for subjects ≥50 kg to achieve an optimal dose of NBI-98854 for each subject. To maintain the study blind, subjects randomized to placebo in each weight group will be subjected to the same dose escalation requirements but will receive only placebo during the treatment period.

Dose escalations will occur at the end of Weeks 2 and 4 based on the following 2 criteria: 1) the subject's tics are not sufficiently controlled per physician investigator assessment; and 2) an evaluation by the physician investigator indicates that the subject is tolerating the study drug at the current dose and would likely be able to tolerate the next dose level. During the first 6 weeks of the 12-week double-blind treatment period, the physician investigator may escalate a subject's dose to the next dose level, continue with the subject's current dose, or reduce to the subject's prior tolerated dose (in subjects who have had a dose escalation). After Week 6, subjects will continue to receive their optimized dose of NBI-98854 or placebo for an additional 6-week dose maintenance period. If a subject's optimal dose has already been established at Week 2 (or at Week 4), no further dose escalation will be allowed during the dose optimization period and the subject will continue at that dose until the end of the 12-week treatment period. At any time after Week 2, the physician investigator may decrease the dose to the previous dose for any subject who had a dose escalation and who is unable to tolerate a given dose increase. The subject will continue at that dose until the end of the 12-week treatment period. The investigator may reduce the subject's dose only one time. Subjects who are unable to tolerate the starting dose or resumption of the previous dose will be discontinued from the study. Follow-up assessments will be conducted at the end of Week 14 (2 weeks after the last dose of the study drug).

After providing parental or legal guardian informed consent with signed and witnessed pediatric assent, subjects will be screened to determine eligibility within 28 days (Days -28 to -1) before the start of study drug dosing on Day 1. On Day 1 (baseline), eligible subjects will return to the study center for collection of baseline safety and efficacy assessments, and the collection of a blood sample for subsequent determination of their cytochrome P450 2D6 (CYP2D6) metabolizer status. Subjects who continue to be eligible for the study will then be randomized (1:1) to placebo or NBI-98854, with assigned dose based on weight group at baseline. A 2-week supply of study drug will be dispensed.

Beginning on Day 1, study drug will be administered qd at home at the subject's bedtime under the supervision of the subject's parent/legal guardian. Subjects will continue to self-administer the study drug daily at approximately the same time for the duration of the 12-week treatment period. Subjects will return to the study center at fixed intervals (end of Weeks 2, 4, 6, 8, 10, and 12) for study assessments and dispensing of study drug (Weeks 2, 4, 6, 8, and 10 only). As much as possible, these study visits and the follow-up visit should occur at the same time as the Day 1 (baseline) visit to standardize the time of day for the assessment of efficacy, safety, and plasma exposure. A representative from the study center will call the subject or parent/legal guardian 3 to 7 days after the start of dosing to inquire about any study drug-related issues with respect to compliance or tolerability. All subjects who complete the 12-week treatment period will enter a 2-week follow-up period with a follow-up visit at Week 14 (subjects who terminate early will have Week 14 assessments conducted). Efficacy, safety, and study drug exposure will be assessed at scheduled times throughout the study. The treatment period visits (Weeks 2, 4, 6, 8, 10, and 12) and the follow-up visit (Week 14) will have a visit window of -2 or +3 days. 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.

Efficacy assessments for TS are the Yale Global Tic Severity Scale (YGTSS; primary), Clinical Global Impression of Tourette Syndrome-Improvement scale (CGI-TS-Improvement), Clinical Global Impression of Tics-Severity scale (CGI-Tics-Severity), the Premonitory Urge for Tics Scale (PUTS), and the Gilles de la Tourette Syndrome – Quality of Life Scale for Children and Adolescents (C&A-GTS-QOL). The YGTSS, PUTS, and C&A-GTS-QOL will be administered at screening, on Day 1 (baseline), and at Weeks 2, 4, 6, 8, 10, 12, and 14 (final study visit or at early termination). At screening and Day 1 (baseline), the CGI-Tics-Severity scale will be used, and then both the CGI-TS-Improvement and CGI-Tics-Severity will be used to rate the overall severity and improvement of tics at Weeks 2, 4, 6, 8, 10, 12, and 14 (final study visit or at early termination).

The YGTSS will serve as the primary assessment of tic behaviors associated with TS. 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 a trained and certified rater (eg, 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. An external video reviewer, not affiliated with the site, will access the central server to view the recording and 1) confirm the subject's TS severity is at least moderate based on a CGI-Tics-Severity of ≥4 (at screening only), and 2) determine if the YGTSS interview program was administered properly. The computer software system for the YGTSS administration, Rater Station™ (Bracket Global, LLC; Philadelphia, PA), will prompt the 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. Safety assessments including adverse event (AE) monitoring, clinical laboratory tests (hematology, clinical chemistry, and urinalysis), vital sign measurements, physical examinations, 12-lead electrocardiogram (ECG), Columbia-Suicide Severity Rating Scale (C-SSRS, Children's Version), Children's Depression Rating Scale - Revised (CDRS-R), the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS), the Attention-Deficit Hyperactivity Disorder Rating Scale-5: Home Version (ADHD Rating Scale-5), and Extrapyramidal Symptom Rating Scale-Abbreviated (ESRS-A) will also be collected at scheduled times throughout the study. Blood samples for plasma drug and metabolite concentration analyses will be at Day 1 (baseline) and at Weeks 2, 4, 6, 8, 10, 12, and 14 (final study visit or at early termination). Subjects/caregivers will be asked to record and provide dosing times from the evening before the treatment period visits when pharmacokinetic (PK) samples are collected.
Study Population: Approximately 120 male and female pediatric subjects (6 to 17 years of age) with a DSM-IV or -V diagnosis of TS; approximately 60 subjects <50 kg and 60 subjects ≥50 kg will be enrolled into this study. The subjects must have at least moderate current TS symptoms, as defined by a CGI-Tics-Severity score of ≥4 (ie, moderately ill) at screening. Subjects with Tourette's spectrum diagnoses (eg, obsessive-compulsive disorder [OCD], attention-deficit hyperactivity disorder [ADHD], etc) must have a stable psychiatric status at screening as determined by the physician investigator.
Duration of Treatment and Study Participation: The expected duration of study participation for each subject is approximately 18 weeks, including up to 28 days of screening, a 12-week double-blind treatment period, and 2 weeks of follow-up, or early termination.
Investigational Product, Dose, and Mode of Administration: NBI-98854 will be supplied as capsules containing 20 mg or 40 mg of NBI-98854 (free base equivalent). Subjects must swallow the capsules at bedtime with at least 4 ounces of water with or without food.
Reference Therapy, Dose, and Mode of Administration: Matching placebo capsules are identical in appearance and will be orally administered in a double-blinded manner (2 placebo capsules) per randomization on an identical schedule to those receiving NBI-98854. Subjects must swallow the capsules at bedtime with at least 4 ounces of water.

Criteria for Evaluation:

Efficacy: The following efficacy assessments will be administered at screening, Day 1 (baseline), and at Weeks 2, 4, 6, 8, 10, 12, and 14 (final study visit or at early termination):

- YGTSS; TTS as the primary assessment
- PUTS
- C&A-GTS-QOL.

The CGI-Tics-Severity will be used to rate the overall severity of tics beginning at screening and Day 1 (baseline), and then both CGI-Tics-Severity and CGI-TS-Improvement will be administered at Weeks 2, 4, 6, 8, 10, 12, and 14 (final study visit or at early termination).

Pharmacokinetics: Blood samples for plasma study drug and metabolite concentration analyses will be collected at Day 1 (baseline) and at Weeks 2, 4, 6, 8, 10, 12, and 14 (final study visit or early termination). Subjects/caregivers will be asked to record and provide dosing times from the evening before the treatment period visits when PK samples are collected.

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

- AEs
- Clinical laboratory tests (hematology, clinical chemistry, and urinalysis)
- Serum prolactin
- Vital signs (including orthostatic systolic and diastolic blood pressure, orthostatic pulse rate, respiratory rate, and oral body temperature)
- Physical examinations (including height and weight)
- 12-lead ECGs
- C-SSRS, Children's Version
- CDRS-R
- CY-BOCS
- ADHD-5 Rating Scale
- ESRS-A.

Statistical Methods: The primary efficacy endpoint is the change from baseline (Day 1) to the end of Week 12 in the YGTSS TTS as generated by the certified site rater using the Rater Station™. The secondary efficacy endpoints are: change from baseline to the end of Week 12 in CGI-Tics-Severity score, TTS responder status at Week 12 (a responder is defined as having a ≥30% reduction in TTS from baseline), and CGI-TS-Improvement responder status at Week 12 (a responder is defined as having a CGI-TS-Improvement score of either a 1 ["very much improved"] or 2 ["much improved"]). Exploratory efficacy endpoints will include the change from baseline to the end of Week 12 for the PUTS total score, CGI-TS-Improvement score at the end of Week 12, change from baseline to the end of Week 12 for the C&A-GTS-QOL score, as well as changes from baseline to the end of Week 12 for the Global Tic Severity and Impairment scores from the YGTSS. Efficacy data will also be summarized from other timepoints (eg, Weeks 2 through 10).

Statistical comparisons between NBI-98854 and placebo will be performed for the efficacy endpoints for the pooled weight groups (<50 kg, ≥50 kg) and data will also be summarized for each weight group separately. The analyses will include comparisons at specified timepoints. The primary analysis of the YGTSS TTS change from baseline will be a mixed-effect model repeated measures (MMRM) analysis of the pooled weight groups including the scores at Weeks 2, 4, 6, 8, 10, and 12 based on the full analysis set (FAS). Supplemental sensitivity analyses of the primary efficacy endpoint will also be conducted.

Safety and plasma study drug and metabolite concentration data will be summarized for the pooled weight groups and each weight group separately, using descriptive statistics.

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADHD	Attention-Deficit Hyperactivity Disorder
ADHD Rating Scale-5	Attention-Deficit Hyperactivity Disorder Rating Scale-5: Home Version
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration versus time curve
$AUC_{0-\infty}$	AUC from 0 hours extrapolated to infinity
β-hCG	β-human chorionic gonadotropin
C&A-GTS-QOL	Gilles de la Tourette Syndrome – Quality of Life Scale for Children and Adolescents
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 scale
CGI-TS-Improvement	Clinical Global Impression of Tourette Syndrome-Improvement scale
C_{max}	Maximum plasma concentration
CMH	Cochran-Mantel-Haenszel
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 4th or 5th Editions
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EDTA K_2	Dipotassium ethylenediaminetetraacetic acid
ESRS-A	Extrapyramidal Symptom Rating Scale-Abbreviated
FAS	Full analysis set
FDA	[United States] Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
HBsAg	Hepatitis B surface antigen
HCV-Ab	Hepatitis C virus antibody
HIV-Ab	Human immunodeficiency virus antibody
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IRB	Institutional Review Board
IWRS	Interactive Web Response System

MAOI	Monoamine oxidase inhibitor
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect model repeated measures
NBI	Neurocrine Biosciences, Inc.
PD	Pharmacodynamics
PK	Pharmacokinetic(s)
PP	Per-protocol
PUTS	Premonitory Urge for Tics Scale
QTcF	Corrected QT interval using Fridericia's formula
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	System organ class
$t_{½}$	Terminal half life
TD	Tardive dyskinesia
TEAE	Treatment-emergent adverse event
t_{max}	Time to maximum plasma concentration
TS	Tourette syndrome
TTS	Total Tic Score
ULN	Upper limit of normal
US	United States
VMAT2	Vesicular monoamine transporter 2
WBC	White blood cell
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 of Technical Requirements for the Registration of Pharmaceuticals for Human Use [ICH; current version]).
- United States (US) Code of Federal Regulations (CFR) dealing with clinical studies (21 CFR parts 50, 54, 56, 312, and 314).
- Guidance for Clinical Trial Sponsors: Clinical Trial Applications, Effective 29 May 2013, Health Canada Therapeutic Products Directorate, Health Products and Food Branch.

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

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

Persistent tics can have a significant impact on patient quality of life and often lead to impaired psychosocial functioning. Some of these problems include social isolation, bullying, physical discomfort (with pain or injury), and poor academic performance (Roessner et al., 2013). Psychosocial stressors can, in turn, exacerbate tic symptomatology. It is under these conditions

that pharmacological interventions are often considered (Chen et al., 2012; Shprecher 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 selective, orally active VMAT2 inhibitor developed by NBI. NBI-98854 is under development for the treatment of TS. NBI-98854 was approved by the US Food and Drug Administration (FDA) in April 2017 for the treatment of adults with tardive dyskinesia (TD), under the trade name INGREZZA®.

In nonclinical studies, NBI-98854 appears to cause little or no cytochrome P450 (CYP) enzyme inhibition or induction at pharmacologically relevant concentrations. NBI-98854 is a moderate inhibitor of P-glycoprotein (P-gp), but only at concentrations that could be achieved in the gastrointestinal (GI) tract and is not an inhibitor of a panel of other drug transporters. Metabolism of NBI-98854 is characterized by hydrolysis of NBI-98854 to NBI-98782, and CYP3A4/5-dependent mono-oxidation to NBI-136110. NBI-98782 is metabolized in part by CYP2D6. All 3 entities, namely, NBI-98854, NBI-98782, and NBI-136110, can bind to and inhibit VMAT2. However, NBI-98782 is the most potent and appears to be responsible for most of the observed pharmacological activity of VMAT2 inhibition.

NBI-98854 appears to be rapidly absorbed with a time to maximum plasma concentration (t_{max}) typically ranging from approximately 0.5 to 1.0 hours. NBI-98854 reaches steady state within 1 week. The active metabolite NBI-98782 gradually forms with a t_{max} of 4 to 8 hours and both NBI-98854 and NBI-98782 are eliminated with a terminal half-life ($t_{½}$) of 15 to 22 hours. Coadministration of ketoconazole (strong CYP3A4/5 inhibitor) with NBI-98854 led to a 1.5- and 1.6-fold increase in the maximum plasma concentration (C_{max}) of NBI-98854 and NBI-98782, respectively, and a 2.1-fold increase in the area under the plasma concentration versus time curve (AUC) from 0 hours extrapolated to infinity ($AUC_{0-\infty}$) of NBI-98854 and NBI-98782. Coadministration of NBI-98854 and rifampin (strong CYP3A4/5 inducer) led to an approximate 30% and 70% decrease in C_{max} and $AUC_{0-\infty}$, respectively, for valbenazine, and an approximate 50% and 80% decrease, respectively, for NBI-98782 compared with administration of NBI-98854 alone. Coadministration of NBI-98854 80 mg and 0.5 mg digoxin resulted in an approximate 1.9-fold increase in the C_{max} of digoxin. The effect of NBI-98854 on digoxin $AUC_{0-\infty}$ was modest (1.4-fold increase) and the mean $t_{½}$ of digoxin was similar with and without NBI-98854 administration. Midazolam C_{max} and $AUC_{0-\infty}$ were similar with and without NBI-98854 administration.

NBI-98854 for the treatment of TS has been evaluated in 3 completed Phase 1b and Phase 2 studies in patients with TS. These include 2 studies in pediatric subjects (NBI-98854-1403 and NBI-98854-1501) and 1 study in adults (NBI-98854-1505). The initial Phase 1b, open-label, multiple-dose study of the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of NBI-98854 (NBI-98854-1403) was conducted in children (6 to 11 years of age) and adolescents (12 to 18 years of age) with TS. Doses of NBI-98854 5 mg and 10 mg were administered in children and doses of NBI-98854 10 mg, 25 mg, or 50 mg were administered in adolescents daily over a 14-day treatment period following a multiple ascending dose protocol. Study NBI-98854-1501 was 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 (qd) for 6 weeks in 98 pediatric subjects with TS. Subjects within each age group were randomized in a 1:1:1 ratio to placebo or 1 of the 2 NBI-98854 doses. Study NBI-98854-1505 was 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 qd for 8 weeks in 124 adult subjects with TS. Subjects were randomized in a 1:1:1 ratio to placebo or 1 of the 2 NBI-98854 doses.

PD results from NBI-98854-1403 revealed reductions from baseline (Day -1) to Day 14 in the Yale Global Tic Severity Scale (YGTSS) total tic score (TTS) in both children and adolescents, and this decrease was observed irrespective of dose. The mean point reduction in TTS for all subjects across all doses tested was -9.4 points at Day 14, which represents a 31% decrease from the mean baseline score. Mean reductions from baseline were also observed in the YGTSS impairment score for both age groups. The Phase 2, NBI-98854-1501 study in children and adolescents did not meet its primary efficacy endpoint of a significant change from baseline to Week 6 in the TTS between the placebo and active groups. A comprehensive exposure-response analysis indicated that the doses selected for this study were too low to provide adequate plasma exposures for tic reduction in most pediatric subjects. For the subset of subjects with NBI-98854 exposures in the relevant range, there was a reduction in tics (range: -11.3 to -13.7 points on the TTS) compared with the subset of subjects with sub-therapeutic exposures (range: -4.7 to -8.3 points on the TTS). Although the efficacy results in participating adults in the NBI-98854-1505 study showed an improvement in overall symptoms of TS as measured by the secondary endpoint, Clinical Global Impression of Change ($p=0.015$ [nominal]), the prespecified primary endpoint, the change from baseline in the YGTSS at Week 8 was not met ($p=0.18$).

NBI-98854 has been generally well tolerated in single doses up to 300 mg and in multiple doses of up to 100 mg in healthy volunteers and patients with TD. Over 850 subjects have been exposed to NBI-98854 in TD clinical studies. In TS patients, safety results from NBI-98854-1403 show that the doses were well tolerated in both child and adolescent age groups. There were no deaths or serious adverse events (SAEs) reported during the study and no child discontinued due to an adverse event (AE). Two adolescents (both in the NBI-98854 50 mg group) discontinued due to AEs. One subject discontinued on Day 2 due to the AEs of agitation, headache, visual impairment, vomiting, and worsening of bradycardia and the other subject discontinued on Day 4 due to the AEs of increased anxiety and insomnia. Preliminary safety results from the Phase 2, NBI-98854-1501 pediatric study suggest that all doses tested

(NBI-98854 10 mg and 20 mg in children and NBI-98854 20 mg and 40 mg in adolescents) were well tolerated in these pediatric subjects with TS. The most frequently reported AEs were headache, somnolence, upper respiratory tract infection, insomnia, and sedation. There were no deaths and only one SAE in the placebo group (conversion disorder). Preliminary results from NBI-98854-1505 showed that the most frequently reported AEs were somnolence (20.2% NBI-98854-treated subjects and 2.5% of placebo subjects), fatigue (14.3% NBI-98854 and 2.5% placebo), and akathisia (13.1% NBI-98854 and 0% placebo). Seventeen subjects (13.7%) discontinued from the study due to AEs, and most of these subjects received NBI-98854 80 mg (13/17 subjects) and the most common reason for AE discontinuation was akathisia (reported in 5 subjects). Four subjects experienced SAEs during the study; the SAEs included pelvic inflammatory disease (placebo subject; moderate and not related to NBI-98854), pneumothorax (80 mg subject; moderate and unlikely related to NBI-98854), hypersensitivity (80 mg subject; moderate and possibly related to NBI-98854), and pneumonia streptococcal, septic shock, renal failure acute, and brachial plexus injury (40 mg subject; severe and unlikely related to NBI-98854).

5.3. Study and Dose Rationale

This is a Phase 2b, randomized, double-blind, placebo-controlled, dose-optimization study to evaluate the efficacy, safety, and tolerability of NBI-98854 titrated to the subject's optimal dose in the range of 20 mg to 60 mg for subjects <50 kg and 40 mg to 80 mg for subjects ≥50 kg compared to placebo, administered qd for a total of 12 weeks of treatment in pediatric subjects with TS. Subjects must have at least moderate current TS symptoms, as defined by a Clinical Global Impression of Tics-Severity scale (CGI-Tics-Severity) score of ≥4 (ie, moderately ill) at screening.

Rationale for Dose Selection and Regimen

Subjects will be randomized in a double-blind manner to qd doses of NBI-98854 for 12 weeks. For subjects randomized to active treatment, the starting dose will be NBI-98854 20 mg for subjects <50 kg and NBI-98854 40 mg for subjects ≥50 kg, which may be escalated in increments of 20 mg every 2 weeks to a maximum of 60 mg for subjects <50 kg and 80 mg for subjects ≥50 kg to achieve an optimal dose of NBI-98854 for each subject.

The current starting doses of NBI-98854 (ie, 20 mg or 40 mg) have been well tolerated in previous studies in pediatric subjects with TS (NBI-98854-1403 and NBI-98854-1501). The dose optimization scheme based on efficacy, tolerability, and safety assessments, as well as bedtime dosing will allow subjects to potentially receive an optimal dose (ie, one that is both well tolerated and efficacious) during the treatment period. Furthermore, the intermediate and high doses have been predicted to potentially provide adequate plasma levels of NBI-98782 for a greater proportion of subjects to achieve clinically meaningful tic suppression based on exposure-response modeling.

6. STUDY OBJECTIVES

The objectives of this clinical study are as follows:

Primary:

- To evaluate the efficacy of NBI-98854, titrated to the subject's optimal dose in the range of 20 mg to 60 mg for subjects <50 kg and 40 mg to 80 mg for subjects ≥50 kg, administered qd for the treatment of TS.

Secondary:

- To evaluate the safety and tolerability of NBI-98854, titrated to the subject's optimal dose in the range of 20 mg to 60 mg for subjects <50 kg and 40 mg to 80 mg for subjects ≥50 kg, administered qd.
- To evaluate plasma exposure measures of NBI-98854 and its active metabolite, NBI-98782, following titrated doses of NBI-98854 from 20 mg to 60 mg for subjects <50 kg and 40 mg to 80 mg for subjects ≥50 kg.

7. OVERVIEW OF STUDY DESIGN

This is a Phase 2b, randomized, double-blind, placebo-controlled, dose-optimization study to evaluate the efficacy, safety, and tolerability of NBI-98854 titrated to the subject's optimal dose in the range of 20 mg to 60 mg for subjects <50 kg at baseline and 40 mg to 80 mg for subjects ≥50 kg at baseline compared to placebo, administered qd for a total of 12 weeks of treatment in pediatric subjects with TS. Approximately 120 male and female pediatric subjects, 6 to 17 years of age, with a Diagnostic and Statistical Manual of Mental Disorders, 4th or 5th Editions (DSM-IV or -V) diagnosis of TS will participate. There will be an approximately equal distribution of subjects in each weight group, <50 kg and ≥50 kg, enrolled into the study and subjects will be stratified based on their weight. Eligible subjects will be randomized in a 1:1 ratio to NBI-98854 or placebo treatment as shown in Table 1.

Table 1: Treatment by Weight Group

Weight Group **Assigned Treatment**	**Number of Subjects (approximate)**
Subjects <50 kg at baseline	
Placebo	30
NBI-98854 (20 to 60 mg)	30
Subjects ≥50 kg at baseline	
Placebo	30
NBI-98854 (40 to 80 mg)	30

For subjects randomized to active treatment, the starting dose will be NBI-98854 20 mg for subjects <50 kg at baseline and NBI-98854 40 mg for subjects ≥50 kg at baseline, which may be escalated in increments of 20 mg every 2 weeks to a maximum of 60 mg for subjects <50 kg and 80 mg for subjects ≥50 kg to achieve an optimal dose of NBI-98854 for each subject. To

maintain the study blind, subjects randomized to placebo in each weight group will be subjected to the same dose escalation requirements, but will receive only placebo during the treatment period. Dose escalations will occur at the end of Weeks 2 and 4 based on the following 2 criteria: 1) the subject's tics are not sufficiently controlled per physician investigator assessment; and 2) an evaluation by the physician investigator indicates that the subject is tolerating the study drug at the current dose and would likely be able to tolerate the next dose level. During the first 6 weeks of the 12-week double-blind treatment period, the physician investigator may escalate a subject's dose to the next dose level, continue with the subject's current dose, or reduce to the subject's prior tolerated dose (in subjects who have had a dose escalation). After Week 6, subjects will continue to receive their optimized dose of NBI-98854 or placebo for an additional 6-week dose maintenance period. If a subject's optimal dose has already been established at Week 2 (or at Week 4), no further dose escalation will be allowed during the dose optimization period and the subject will continue at that dose until the end of the 12-week treatment period. At any time after Week 2, the physician investigator may decrease the dose to the previous dose for any subject who had a dose escalation and who is unable to tolerate a given dose increase. The subject will continue at that dose until the end of the 12-week treatment period. The investigator may reduce the subject's dose only one time. Subjects who are unable to tolerate the starting dose or resumption of the previous dose will be discontinued from the study. Follow-up assessments will be conducted at the end of Week 14 (2 weeks after the last dose of the study drug).

After providing parental or legal guardian informed consent with signed and witnessed pediatric assent, subjects will be screened to determine eligibility within 28 days (Days -28 to -1) before the start of study drug dosing on Day 1. On Day 1 (baseline), eligible subjects will return to the study center for collection of baseline safety and efficacy assessments, and the collection of a blood sample for subsequent determination of their CYP2D6 metabolizer status. Subjects who continue to be eligible for the study will then be randomized (1:1) to placebo or NBI-98854, with assigned dose based on weight group at baseline. A 2-week supply of study drug will be dispensed.

Beginning on Day 1, study drug will be administered qd at home at the subject's bedtime under the supervision of the subject's parent/legal guardian. Subjects will continue to self-administer the study drug daily at approximately the same time for the duration of the 12-week treatment period. Subjects will return to the study center at fixed intervals (end of Weeks 2, 4, 6, 8, 10, and 12) for study assessments and dispensing of study drug (Weeks 2, 4, 6, 8, and 10 only). As much as possible, these study visits and the follow-up visit should occur at the same time as the Day 1 (baseline) visit to standardize the time of day for the assessment of efficacy, safety, and plasma exposure. A representative from the study center will call the subject or parent/legal guardian 3 to 7 days after the start of dosing to inquire about any study drug-related issues with respect to compliance or tolerability. All subjects who complete the 12-week treatment period will enter a 2-week follow-up period with a follow-up visit at Week 14 (subjects who terminate early will have Week 14 assessments conducted). Efficacy, safety, and study drug exposure will be assessed at scheduled times throughout the study. The treatment period visits (Weeks 2, 4, 6, 8, 10, and 12) and the follow-up visit (Week 14) will have a visit window of -2 or +3 days. 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.

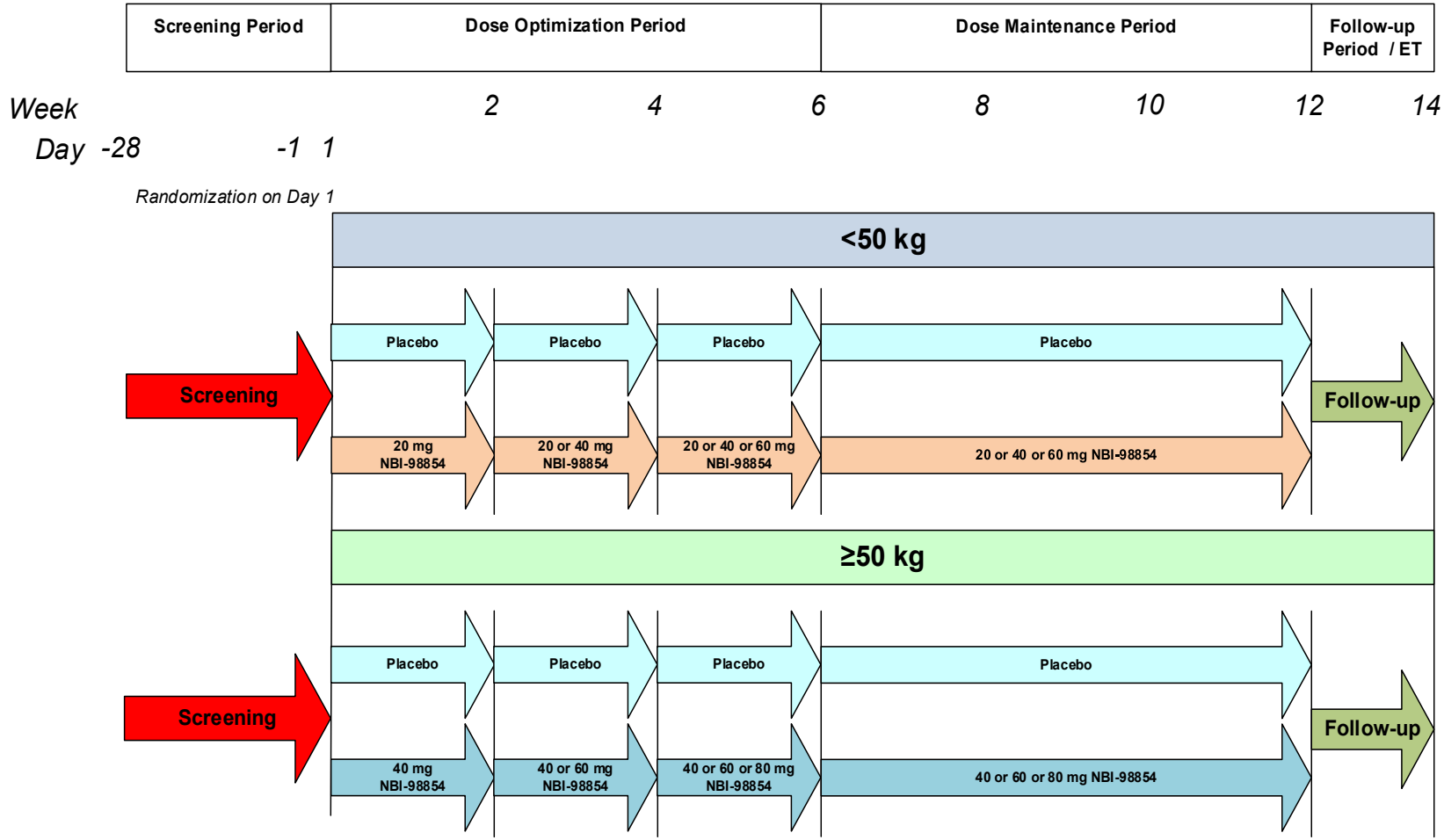
Efficacy assessments for TS are the YGTSS (primary), the CGI-TS-Improvement, CGI-Tics-Severity, the Premonitory Urge for Tics Scale (PUTS), and the Gilles de la Tourette Syndrome – Quality of Life Scale for Children and Adolescents (C&A-GTS-QOL). The YGTSS, PUTS, and C&A-GTS-QOL will be administered at screening, on Day 1 (baseline), and at Weeks 2, 4, 6, 8, 10, 12, and 14 (final study visit or at early termination). At screening and Day 1 (baseline), the CGI-Tics-Severity scale will be used, and then both the CGI-TS-Improvement and CGI-Tics-Severity will be used to rate the overall severity and improvement of tics at Weeks 2, 4, 6, 8, 10, 12, and 14 (final study visit or at early termination).

Safety assessments including AE monitoring, clinical laboratory tests (hematology, clinical chemistry, and urinalysis), vital sign measurements, physical examinations, 12-lead electrocardiogram (ECG), Columbia-Suicide Severity Rating Scale (C-SSRS, Children's Version), Children's Depression Rating Scale - Revised (CDRS-R), the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS), the Attention-Deficit Hyperactivity Disorder Rating Scale-5: Home Version (ADHD Rating Scale-5), and Extrapyramidal Symptom Rating Scale-Abbreviated (ESRS-A) will also be collected at scheduled times throughout the study.

Blood samples for plasma drug and metabolite concentration analyses will be at Day 1 (baseline) and at Weeks 2, 4, 6, 8, 10, 12, and 14 (final study visit or at early termination). Subjects/caregivers will be asked to record and provide dosing times from the evening before the treatment period visits when PK samples are collected.

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

Figure 1: Study Design Schematic



8. STUDY POPULATION

This study will be conducted in approximately 120 male and female pediatric subjects (6 to 17 years of age) with a DSM-IV or -V diagnosis of TS. A total of approximately 60 subjects <50 kg and approximately 60 subjects ≥50 kg will be enrolled into this study. Subjects must meet all the inclusion criteria and none of the exclusion criteria to enter the study.

8.1. Inclusion Criteria

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

1. Have documentation of written and witnessed pediatric assent from the subject and written informed consent from the subject's parents or legal guardian.
2. Be male or female, aged 6 to 17 years, inclusive.
3. Be in good general health, as determined by medical history, physical examination, clinical laboratory assessments, and 12-lead ECG.
4. Have a DSM-IV or -V diagnosis of TS.
5. Have at least moderate current tic severity, as defined by a CGI-Tics-Severity score of ≥4 (ie, moderately ill) at screening. This determination must be independently confirmed by the external video reviewer using a video recording of the subject's YGTSS assessment administered at the clinical site by a trained and certified rater.
6. Have TS symptoms that cause marked distress or significant impairment in school, occupational, and/or social function.
7. Subjects must have a stable psychiatric status (such as TS spectrum diagnoses [eg, obsessive-compulsive disorder, ADHD]) as clinically determined by the investigator.
8. If medications are being used to treat TS symptoms and/or TS spectrum diagnoses, subjects must be on stable doses of these medications for a minimum of 30 days before Day 1 (baseline), and the medication regimen is expected to remain stable throughout the study period. The use of concomitant dopamine antagonists (eg, pimozide, haloperidol, aripiprazole) and/or tetrabenazine to treat TS symptoms is prohibited. Other nondopaminergic tic suppression therapy (eg, clonidine, guanfacine) is allowed during the study period if the dose regimen has been stable for a minimum of 30 days before Day 1 (baseline).
9. Subjects with stable medical conditions requiring medications that are not prohibited per protocol must be on stable doses of these medications for a minimum of 30 days before Day 1 (baseline), and the medication regimen is expected to remain stable throughout the study period.
10. Subjects of childbearing potential must agree to use contraception consistently from screening until 30 days (females) or 90 days (males) after the last dose of study drug. A female subject of childbearing potential is defined as a female capable of becoming pregnant, which includes subjects who have had their first menstrual cycle (ie, menarche) and are not surgically sterile (ie, bilateral oophorectomy, hysterectomy or bilateral tubal

ligation for at least 3 months prior to screening). A male subject of childbearing potential is defined as a subject who has reached spermarche and has not been vasectomized for at least 3 months prior to screening.

Acceptable methods of contraception include the following:

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

Subjects who practice total abstinence from sexual intercourse as the preferred lifestyle are not required to use contraception (periodic abstinence is not acceptable).

11. Female subjects of childbearing potential must have a negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test at screening and negative urine pregnancy test at Day 1 (baseline).
12. Have a body weight (in kg) greater than or equal to the 5th percentile of his/her age- and gender-matched weight percentile at screening.
13. Adolescent subjects (12 to 17 years of age) must have a negative urine drug screen (negative for amphetamines, barbiturates, benzodiazepines, phencyclidine, cocaine, opiates, or cannabinoids) at screening (based on results from central laboratory) and Day 1 (baseline; based on results from on-site urine drug screen kit). Subjects who are on stable doses of prescribed and supervised (not as needed [prn]) benzodiazepines, opiates, or psychostimulants (for subjects with comorbid ADHD) can participate in the study.
14. Adolescent subjects (12 to 17 years of age) must have a negative alcohol breath test at screening and Day 1 (baseline).
15. 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 center and return for the follow-up visit.

8.2. Exclusion Criteria

Subjects will be excluded from the study if they:

1. Have an unstable medical condition or chronic disease (including significant neurological, hepatic, renal, cardiovascular, gastrointestinal, pulmonary, or endocrine disease), or malignancy that could confound interpretation of study outcome.
2. Had a medically significant illness within 30 days of screening.
3. Excessive use of tobacco and/or nicotine-containing products (based on the investigator's assessment) within 30 days of screening.

4. Have a history of substance (drug or alcohol) dependence or abuse within the 3 months before Day 1 (baseline), as defined in the DSM-IV (Substance Dependence or Abuse) or DSM-V (Substance Use Disorder).
5. Are currently pregnant or lactating.
6. Have a known history of neuroleptic malignant syndrome.
7. Have a known history of long QT syndrome or cardiac arrhythmia.
8. Have a screening or Day 1 average triplicate ECG corrected QT interval using Fridericia's formula (QTcF) of >450 msec or the presence of any clinically significant cardiac abnormality.
9. Have serum creatinine levels greater than the upper limit of normal (ULN) at screening, or aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), or total bilirubin >1.5 times the ULN at screening. Subjects with a documented diagnosis of Gilbert's syndrome are not required to meet the bilirubin criteria.
10. 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 $<100,000/mm^3$.
11. Have a hematologic malignancy or solid tumor diagnosed within 3 years prior to screening, except for localized skin cancer or carcinoma in situ of the cervix.
12. Have biochemistry or hematology not within the laboratory's reference range and deemed by the investigator to be clinically significant at screening.
13. Have a positive human immunodeficiency virus antibody (HIV-Ab) test result, hepatitis B surface antigen (HBsAg) test result, or hepatitis C virus antibody (HCV-Ab) with confirmatory positive polymerase chain reaction reflex test result at screening.
14. Have received any investigational product within a time period equal to 5 half-lives of the product, if known, or a minimum of 30 days before screening, whichever is longer, or plan to use an investigational drug (other than NBI-98854) during the study.
15. Have received any excluded concomitant medication as detailed in Section 9.8.1.
16. Have initiated Comprehensive Behavioral Intervention for Tics (CBIT) during the screening period or at Day 1 (baseline) or plan to initiate CBIT during the study.
17. Have a blood loss ≥250 mL or donated blood within 56 days or donated plasma within 7 days of Day 1 (baseline).
18. Have a significant risk of suicidal or violent behavior. Subjects with any lifetime suicidal behavior, or suicidal ideation of type 4 (active suicidal ideation with some intent to act, without specific plan) or type 5 (active suicidal ideation with specific plan and intent) in the past year before screening based on the C-SSRS Children's Version should be excluded.
19. Have an allergy, hypersensitivity, or intolerance to VMAT2 inhibitors (eg, tetrabenazine).
20. Have a history of or suspected poor compliance in clinical research studies.

21. Have previous experience with NBI-98854 or previously participated in an NBI-98854 clinical study.

8.3. Subject Identification and Replacement

Subjects will be identified by their unique subject number and initials (first, middle, last; a hyphen may be used if the subject has no middle name). The subject initials and subject number will be noted on electronic case report forms (eCRFs), all source documentation, laboratory documents, and ECG tracings. Subjects who discontinue from the study will not be replaced.

8.4. Randomization

An Interactive Web Response System (IWRS) will be used to randomize subjects to 1 of 2 double-blind treatment assignments within each weight group: placebo or NBI-98854 (starting NBI-98854 dose of 20 mg in subjects <50 kg and 40 mg in subjects ≥50 kg) in a 1:1 ratio. Randomization will occur on Day 1 after the subject is confirmed to have met the eligibility criteria. Treatment assignments will be made per a computer-generated randomization schedule. Investigators or a designee will access the IWRS to obtain randomization assignments.

9. STUDY EVALUATIONS

9.1. Schedule of Assessments

A schedule of assessments that summarizes the frequency and timing of all assessments is provided in Table 2. No protocol-related procedures should be performed before parental or legal guardian informed consent with written and witnessed pediatric assent 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 2: Schedule of Assessments

Procedure[a]	Screening Period	Treatment Period								Follow-up Period
		Day 1[b]		Dose Optimization			Dose Maintenance			Follow-up/ ET
Week	Day -28 to -1	Baseline	Dosing	2	4	6	8	10	12	14[c]
Visit	1	2	--	3	4	5	6	7	8	9
Informed consent/assent	X									
Treatment assignment script/video[d]	X	X								
Inclusion/exclusion criteria	X	update								
Medical history	X	update								
Physical examination (including weight)	X	X		X		X			X	X
Height	X									
Vital signs	X	X		X	X	X	X	X	X	X
12-lead ECG[e]	X	X		X	X	X	X	X	X	X
Pregnancy test[f]	X (s)	X (u)		X (u)	X (u)	X (u)	X (u)	X (u)	X (u)	X (u)
Serology (HBsAg, HCV-Ab and HIV-Ab)	X									
Clinical laboratory tests[g]	X	X		X	X	X	X	X	X	X
Urine drug screen (adolescents)	X	X								
Alcohol breath test (adolescents)	X	X								
Genotype blood sample[h]		X								
Blood sample for prolactin		X		X	X	X	X	X	X	X
Blood sample for PK assessments		X		X	X	X	X	X	X	X
YGTSS (including video recording)	X	X		X	X	X	X	X	X	X
PUTS	X	X		X	X	X	X	X	X	X
CGI-Tics-Severity	X	X		X	X	X	X	X	X	X
CGI-TS-Improvement				X	X	X	X	X	X	X
C-SSRS	X	X		X	X	X	X	X	X	X
CY-BOCS and CDRS-R	X	X		X	X	X	X	X	X	X
ADHD Rating Scale-5: Home Version		X		X	X	X	X	X	X	X
ESRS-A	X	X		X	X	X	X	X	X	X
C&A-GTS-QOL	X	X		X	X	X	X	X	X	X
Randomization		X								
Study drug dosing at home[i]			X	X	X	X	X	X	X	
Dispense study drug		X		X	X	X	X	X		
Study drug accountability[j]				X	X	X	X	X	X	
AE monitoring	X	X	X	X	X	X	X	X	X	X
Prior and concomitant Medications	X	X	X	X	X	X	X	X	X	X
Call to subject[k]				X						

ADHD=attention-deficit hyperactivity disorder; AE=adverse event; C&A-GTS-QOL=Gilles de la Tourette Syndrome – Quality of Life Scale for Children and Adolescents; CDRS-R=Children's Depression Rating Scale - Revised; CGI-Tics-Severity=Clinical Global Impression Tics-Severity scale; CGI-TS-Improvement=Clinical Global Impression of Tourette Syndrome-Improvement scale; 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; ET=early termination; HBsAg=hepatitis B surface antigen; HCV-Ab=hepatitis C virus antibody; HIV-Ab=human immunodeficiency virus antibody; PK=pharmacokinetic; QTcF=corrected QT interval using Fridericia's formula; PUTS=Premonitory Urge for Tics Scale; s=serum; u =urine; YGTSS=Yale Global Tic Severity Scale.

[a] As much as possible, study visits should occur at approximately the same time as the Day 1 visit to standardize the time of day for the assessment of efficacy, safety, and plasma exposure throughout the study period.

[b] Day 1 is the day of baseline assessments and randomization. Day 1 is also the first day of dosing; study drug will be administered at home at bedtime. Visits will have a window of -2 to +3 days.

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

[d] Subjects will be shown the video titled "Your Role in a Clinical Trial, Some Information about Research Studies" (at screening only) and informed about the placebo-controlled design of the study using the treatment assignment script provided by the Sponsor (on Day 1 [baseline] only).

[e] A standard 12-lead ECG will be conducted in triplicate (at least 1 minute apart and within 15 minutes) after the subject has rested supine for at least 5 minutes. The ECG parameters will be based on the ECG machine readings (QTcF may be calculated).

[f] A serum pregnancy test will be conducted at screening and urine pregnancy tests will be conducted at all other study visits for female subjects of childbearing potential.

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

[h] Blood sample for genotyping will be analyzed for enrolled subjects only.

[i] Study drug will be administered once daily at the subject's bedtime at home under the supervision of their parent/guardian. The date and time of each dosing of study drug will be recorded.

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

[k] Sites are to call subjects within 3 to 7 days from Day 1 to inquire about compliance or tolerability issues.

9.2. Screening and Baseline Assessments

9.2.1. Genotyping

On Day 1 (baseline), a blood sample will be collected from enrolled subjects for the analysis of CYP2D6 status (ie, normal, intermediate, poor, or ultra-rapid metabolizers). Approximately 4 mL of blood will be collected in tubes containing dipotassium ethylenediaminetetraacetic acid (EDTA K_2). After the sample is obtained, it should be thoroughly mixed. The vials will be stoppered and labeled with the study barcode and subject number. The samples will be stored at approximately -20°C within approximately 15 minutes of collection. The collection and submission of medical information will be accomplished with strict adherence to professional standards of confidentiality. Genotyping blood samples collected from subjects will be shipped to a central laboratory for analysis.

9.3. Efficacy Assessments

9.3.1. Yale Global Tic Severity Scale

The YGTSS will serve as the primary assessment of tic behaviors associated with TS (Leckman et al., 1989). The YGTSS is designed to rate the overall severity of motor and phonic tic symptoms across a range of dimensions: number, frequency, intensity, complexity, and interference. The scale also includes an impairment assessment. The YGTSS will be administered by the investigator (or qualified designee) using a computer-based structured clinical interview. At each timepoint, the YGTSS interview will be video recorded. The video recording will follow a standardized set of guidelines and the recorded video will be uploaded to a secure central server. An external video reviewer, not affiliated with the site, will access the central server to view the recording and 1) confirm the subject's TS severity is at least moderate based on a CGI-Tics-Severity of ≥4 (at screening only), and 2) determine if the YGTSS interview program was administered properly. The computer software system for the YGTSS administration, Rater Station™ (Bracket Global, LLC; Philadelphia, PA), will prompt the investigator (or a qualified designee), a trained and certified rater, to enter a score for each item of the scale based on subject and parent responses during the structured clinical interview. As much as possible, a given subject should have the same rater throughout the study. The software will also generate individual scores for each item of the scale (tandem rating) and will generate the TTS and the Global Tic Severity Score.

The YGTSS will be administered at screening, Day 1 (baseline), Weeks 2, 4, 6, 8, 10, 12, and at the final follow-up visit (Week 14), or early termination. A copy of the YGTSS is provided in Appendix 17.1.

9.3.2. 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 pretic (ie, premonitory) urges along with relief that may be experienced after tics have been completed.

The investigator (or designee) will administer the PUTS at screening, Day 1 (baseline), Weeks 2, 4, 6, 8, 10, 12 and at the final follow-up visit (Week 14), or early termination. A copy of the PUTS is provided in Appendix 17.2.

9.3.3. Clinical Global Impression Scales

The CGI-Tics–Severity and CGI-TS–Improvement 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 screening, Day 1 (baseline), Weeks 2, 4, 6, 8, 10, 12 and at the final follow-up visit (Week 14), or early termination. A copy of the CGI-Tics-Severity scale is provided in Appendix 17.3.

The CGI-TS–Improvement scale will be used to assess overall improvement since the initiation of study drug dosing on a 7-point scale (range; 1=very much improved to 7=very much worse). CGI-TS-Improvement scales will be assessed by the investigator at Weeks 2, 4, 6, 8, 10, 12 and at the final follow-up visit (Week 14), or early termination. A copy of the CGI-TS-Improvement scale is provided in Appendix 17.4.

9.3.4. Gilles de la Tourette Syndrome-Quality of Life for Children and Adolescents

The C&A-GTS-QOL is a valid and reliable instrument to assess the quality of life in children and adolescents with TS (Cavanna et al., 2013). It consists of 27 items and 4 subscales (psychological, physical, obsessive-compulsive, and cognitive). Each item is rated across 5 response options: "Never," "Rarely," "Sometimes," "Often," and "Always." There are 2 versions of this instrument: 1 version for children aged 6 to 12 years and 1 version for adolescents aged 13 to 18 years. The C&A-GTS-QOL also includes a visual analog scale, assessing how satisfied the subject feels with his/her life (range of 0 to 100, with 100 representing the greatest satisfaction).

The subject will complete the C&A-GTS-QOL at screening, Day 1 (baseline), Weeks 2, 4, 6, 8, 10, 12 and at the final follow-up visit (Week 14), or early termination. The subject can receive assistance filling out the questionnaire if needed. Copies of both versions of the C&A-GTS-QOL are provided in Appendix 17.5.

9.4. Pharmacokinetic Evaluations

Blood samples to evaluate plasma concentrations of NBI-98854 and the metabolite NBI-98782 will be collected at Day 1 (baseline) and at Weeks 2, 4, 6, 8, 10, 12 and at the final follow-up visit (Week 14), or early termination. The exact time of collection will be recorded on the eCRF.

For each plasma sample, approximately 2 mL of blood will be collected in tubes containing EDTA K_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 2000 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 and primary or back-up sample designation (PK A and PK B, respectively). The samples will be stored at approximately -20°C within approximately 15 minutes of centrifugation. The date and actual 24-hour clock time of each collection will be recorded on the eCRF. The duplicate plasma sample at each timepoint will be stored and used as backup. These samples (including a manifest with additional information) will be shipped to a central laboratory for analysis to be stored at approximately -70°C. Plasma samples remaining at the end of the study may be used for exploratory assessments.

9.5. Safety Assessments

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

Any abnormal vital sign measurement, physical examination finding, clinical laboratory test, or ECG parameter deemed clinically significant by the investigator will be repeated, including test results obtained 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, ADHD Rating Scale-5, or clinical assessment), the finding will be documented as an AE, and appropriate psychiatric evaluation and intervention will be provided.

9.5.1. Data Safety Monitoring Board

An independent DSMB will periodically review ongoing unblinded 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.

9.5.2. Vital Sign Measurements

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

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

9.5.3. Medical History

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

9.5.4. Physical Examination, Including Height and Weight

The complete physical examination will consist of an assessment of general appearance, skin and mucosae, head, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest/lungs, cardiovascular, abdomen, extremities, musculoskeletal, and neurological system. A complete physical examination including weight will be performed at screening, Day 1 (baseline), and at Weeks 2, 6, 12, and at the final follow-up visit (Week 14), or early termination. Height will be measured at screening only. Height and weight will be measured with subjects not wearing shoes.

9.5.5. Electrocardiogram

A standard 12-lead ECG will be recorded in triplicate (at least 1 minute apart and within 15 minutes) after the subject has rested supine for at least 5 minutes. The ECG parameters that will be assessed include heart rate, PR interval, QRS duration, corrected QT interval, and QTcF (machine readings or calculated). Additionally, the occurrence of de- and re-polarization and rhythm disorders or other cardiac abnormalities will be assessed. Based on the review of these parameters, the investigator or designee will note if the ECG is Normal, Abnormal not Clinically Significant, or Abnormal Clinically Significant. If the ECG is Abnormal Clinically Significant, the investigator or designee will provide a description of the abnormality recorded on the AE eCRF.

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

9.5.6. 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 and screening 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 clinical chemistry; adolescents (12 to 17 years of age) – 4 mL for hematology and 5 mL for clinical chemistry (includes screening serum pregnancy tests for female subjects of childbearing potential).

Clinical safety laboratory assessments will be performed at screening, Day 1 (baseline), and at Weeks 2, 4, 6, 8, 10, 12, and at the final follow-up visit (Week 14), or 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, GGT, creatine kinase, total bilirubin, total cholesterol, triglycerides, total protein, and glucose.

Urinalysis: specific gravity, nitrites, 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 nitrites, protein, leukocyte esterase, or blood.

The following additional laboratory tests will be performed:

Serum Prolactin: Blood samples to determine serum prolactin concentration will be collected at Day 1 (baseline), at Weeks 2, 6, 8, 10, 12 and at the final follow-up visit (Week 14), or early termination. Approximately 2.5 mL (children, 6 to 11 years of age) or 5 mL (adolescents, 12 to 17 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. Prolactin results will remain blinded to the investigator.

Serology: Blood will be collected for HIV-Ab, HBsAg, and HCV-Ab testing at screening (as part of clinical chemistry). The results of the anti-HIV-Ab testing will be retained by the study site under confidential restriction. The following approximate amounts will be collected: 9 mL (children, 6 to 11 years of age) or 10 mL (adolescents, 12 to 17 years of age).

Urine Drug Screen and Alcohol Breath Test: The urine drug screen will test for amphetamines, barbiturates, phencyclidine, benzodiazepines, cannabinoids, cocaine, and opiates. Urine testing kits will be provided by the central laboratory for preliminary confirmation of negative drug screen at the site prior to dosing. A separate urine sample will also be sent to the central laboratory for analysis. A urine drug screen and alcohol breathalyzer test will be performed at screening and on Day 1. The urine drug screen and alcohol breathalyzer test will be performed only in adolescent subjects (12 to 17 years of age). A urine drug screen using a kit provided by the central laboratory may be conducted at the clinical site at any time during the study if the subject (adolescent subjects only) is suspected of substance or drug abuse.

Pregnancy Tests: A pregnancy test will be conducted for female subjects of childbearing potential. A serum pregnancy test will be conducted at screening and a urine pregnancy test will be conducted on Day 1, Weeks 2, 4, 6, 8, 10, 12 and at the final follow-up visit (Week 14), or early termination.

9.5.7. Columbia-Suicide Severity Rating Scale Children's Versions

The C-SSRS is a validated instrument to prospectively assess suicidal ideation and behavior (http://www.cssrs.columbia.edu). There are versions of the questionnaire designed for use at screening (Children's Baseline/Screening version) and at baseline and visits throughout the study (Children's Since Last Visit version). All versions of the C-SSRS include a series of screening questions related to suicidal ideation and suicidal behavior. Subject responses of "yes" to one or more screening questions will prompt additional questions that evaluate frequency and intensity of suicidal ideation and/or behavior. Subjects with any lifetime suicidal behavior or suicidal ideation of type 4 (active suicidal ideation with some intent to act, without specific plan) or type 5 (active suicidal ideation with specific plan and intent) in the 1 year before screening based on the C-SSRS Children's version should be excluded (see exclusion criterion #18 in Section 8.2).

The C-SSRS will be administered and scored by the investigator or qualified study center personnel at screening, Day 1 (baseline), and Weeks 2, 4, 6, 8, 10, 12 and at the final follow-up

visit (Week 14), or early termination. A copy of each Children's version of the C-SSRS is provided in Appendix 17.6 and Appendix 17.7, respectively.

9.5.8. 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 screening, Day 1 (baseline), and at Weeks 2, 4, 6, 8, 10, 12 and at the final follow-up visit (Week 14), or early termination. A copy of the CDRS-R is provided in Appendix 17.8.

9.5.9. Children's Yale-Brown Obsessive Compulsive Scale

The CY-BOCS is a semi-structured interview designed to rate the severity of obsessive and compulsive symptoms in children. The investigator (or designee) will administer the CY-BOCS at screening, Day 1 (baseline), Weeks 2, 4, 6, 8, 10, 12, and at the final follow-up visit (Week 14), or early termination. A copy of the CY-BOCS is provided in Appendix 17.9.

9.5.10. 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 2 weeks. The scale comes in 2 versions: child (ages 5 to 10 years) and adolescent (ages 11 to 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 Day 1 (baseline), Weeks 2, 4, 6, 8, 10, 12 and at the final follow-up visit (Week 14), or early termination. A copy of the ADHD Rating Scale-5: Home Version is provided in Appendix 17.10.

9.5.11. Extrapyramidal Symptom Rating Scale-Abbreviated

The ESRS-A is a psychometrically validated instrument that assesses 4 types of movement disorders: parkinsonism, akathisia, dystonia, and dyskinesia (Chouinard and Margolese, 2005). The investigator (or designee) will administer the ESRS-A at screening, Day 1 (baseline), Weeks 2, 4, 6, 8, 10, 12 and at the final follow-up visit (Week 14) or upon early termination. A copy of the ESRS-A is provided in Appendix 17.11.

9.5.12. Estimated Total Blood Sample Volume Required by Study

The estimated total blood sample volume for each subject is presented in Table 3. These estimates include samples to be collected during screening, the treatment period, and the final visit (Week 14 or upon early termination).

Table 3: Estimated Total Blood Sample Volume

Parameter	Number of Samples Required	Approximate Volume (mL)	Approximate Total Volume (mL)
Children (6 to 11 years of age)			
Clinical chemistry[a]	9	2.5	22.5
Hematology	9	3	27
Genotyping	1	4	4
Serology	1	9	9
Serum prolactin	8	2.5	20
Pharmacokinetics	8	2	16
Approximate Maximum Total Blood Sample Volume per Subject (mL):			**98.5**
Adolescents (12 to 17 years of age)			
Clinical chemistry[a]	9	5	45
Hematology	9	4	36
Genotyping	1	4	4
Serology	1	10	10
Serum prolactin	8	5	40
Pharmacokinetics	8	2	16
Approximate Maximum Total Blood Sample Volume per Subject (mL):			**151**

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

9.6. Specific Study Information

After providing parental or legal guardian informed consent with signed and witnessed pediatric assent (as required by the governing IRB), subjects will undergo screening procedures within 28 days of Day -1.

9.6.1. Screening (Days -28 to -1)

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

- Obtain informed consent/pediatric assent.
- Subjects will be shown the video titled “Your Role in a Clinical Trial, Some Information About Research Studies.”
- Assess inclusion/exclusion criteria.
- Collect medical history.
- Perform a physical examination (including height and weight).
- Collect vital signs, including orthostatic systolic and diastolic blood pressures, orthostatic pulse rate, respiratory rate, and body temperature.
- Perform 12-lead ECG in triplicate (at least 1 minute apart and within 15 minutes).
- Perform a serum pregnancy test (β-hCG) only for female subjects of childbearing potential.
- Collect blood sample for serology testing (HIV-Ab, HBsAg, and HCV-Ab).
- Collect blood sample for hematology and clinical chemistry.

- Collect urine sample for urinalysis.
- Perform alcohol breathalyzer test and urine drug screen (both only in adolescent subjects).
- Administer the YGTSS, including video recording.
- Administer the PUTS.
- Administer the CGI-Tics-Severity scale.
- Administer the C-SSRS (Children's Screening/Baseline version).
- Administer the CY-BOCS and CDRS-R.
- Administer the ESRS-A.
- Administer the C&A-GTS-QOL.
- AE monitoring.
- Record prior medications.

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

The following items will also be conducted at screening:

- Instruct subjects of childbearing potential who do not practice total abstinence to continue using contraception (see inclusion criterion #10 in Section 8.1).
- Eligible subjects will be instructed to return to the center on Day 1. The following should be considered for scheduling purposes: as much as possible, visits should occur at approximately the same time as the Day 1 (baseline) visit to standardize the time of day for the assessment of efficacy, safety, and plasma exposure throughout the study period.

9.6.2. Day 1 (Baseline Assessments and Start of Dosing)

Subjects and parents/legal guardians will return to the center on Day 1.

On Day 1, the following baseline study evaluations and tasks will be performed at the study center:

- Subjects will be informed about the placebo-controlled design of the study using the treatment assignment script provided by the Sponsor.
- Update inclusion and exclusion criteria.
- Update medical history.
- Perform a physical examination including weight.
- Collect vital signs, including orthostatic systolic and diastolic blood pressures, orthostatic pulse rate, respiratory rate, and body temperature.
- Perform 12-lead ECG in triplicate (at least 1 minute apart and within 15 minutes).
- Perform a urine pregnancy test only for female subjects of childbearing potential.
- Collect blood sample for hematology and clinical chemistry.
- Collect urine sample for urinalysis.
- Perform alcohol breathalyzer test and urine drug screen (both only in adolescent subjects).

- Collect blood sample for CYP2D6 genotype status (for randomized subjects only).
- Collect blood sample for serum prolactin.
- Collect PK blood sample for NBI-98854 and metabolite concentrations.
- Administer the YGTSS, including video recording.
- Administer the PUTS.
- Administer the CGI-Tics-Severity scale.
- Administer the C-SSRS (Children's Since Last Visit version).
- Administer the CY-BOCS and CDRS-R.
- Administer the ADHD Rating Scale-5.
- Administer the ESRS-A.
- Administer the C&A-GTS-QOL.
- Access the IWRS to obtain randomization assignments for eligible subjects.
- Dispense a 2-week supply of study drug and provide instructions on storage and administration of the study drug.
- Instruct subjects to record the date and time of each dose on the labels provided on the study drug kit packaging form.
- Instruct subjects to begin taking study drug nightly at bedtime under supervision of their parents/legal guardians, beginning on Day 1. (The timing of study drug administration should remain consistent throughout the treatment period.)
- Instruct subjects and parents/legal guardians to return to the study center at Week 2 (-2 to +3 days) and to bring their study drug kit.
- AE monitoring.
- Record concomitant medications.

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

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

Sites are to call subjects within 3 to 7 days after the Day 1 visit to inquire about compliance or tolerability issues. Note, subsequent study visits will be 14 days from the previous visit; for example, the Week 2 visit will be on Day 15 (-2 to +3 days) and the Week 4 visit will be on Day 29 (-2 to +3 days).

9.6.3. Dose Optimization Period: Weeks 2, 4, and 6 (-2 to +3 Days for Each Visit)

Subjects and parents/legal guardians will return to the study center at Weeks 2, 4, and 6.

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

- Perform a physical examination including weight (Weeks 2 and 6 only).

- Collect vital signs, including orthostatic systolic and diastolic blood pressures, orthostatic pulse rate, respiratory rate, and body temperature.
- Perform 12-lead ECG in triplicate (at least 1 minute apart and within 15 minutes).
- Perform a urine pregnancy test only for female subjects of childbearing potential.
- Collect blood sample for hematology and clinical chemistry.
- Collect urine sample for urinalysis.
- Collect blood sample for serum prolactin.
- Collect PK blood sample for NBI-98854 and metabolite concentrations.
- Administer the YGTSS, including video recording.
- Administer the PUTS.
- Administer the CGI-Tics-Severity scale.
- Administer the CGI-TS-Improvement scale.
- Administer the C-SSRS (Children's Since Last Visit version).
- Administer the CY-BOCS and CDRS-R.
- Administer the ADHD Rating Scale-5.
- Administer the ESRS-A.
- Administer the C&A-GTS-QOL.
- Perform compliance check by counting the capsules returned.
- AE monitoring.
- Record concomitant medications.

Dose Escalation Assessment

At the end of Week 2 and Week 4 visits, a dose escalation will occur based on the following 2 criteria: 1) the subject's tics are not sufficiently controlled per physician investigator assessment; and 2) an evaluation by the physician investigator indicates that the subject is tolerating the study drug at the current dose and would likely be able to tolerate the next dose level. Based on these criteria, the physician investigator will choose 1 of the following dosing options:

- Dose escalation, which will occur in 20 mg increments (to maintain the study blind, subjects randomized to placebo will be subjected to the same dose escalation requirements but will receive only placebo during the treatment period):
  - Subjects <50 kg at baseline: from 20 mg to 40 mg (Week 2); from 40 mg to 60 mg (Week 4).
  - Subjects ≥50 kg at baseline: from 40 mg to 60 mg (Week 2); from 60 mg to 80 mg (Week 4).
- Maintenance of current dose (with no further dose increases).
- Dose reduction to previous dose in subjects who have had a dose escalation. The physician investigator may decrease the dose to the previous dose at any time after the end of Week 2

(including between scheduled study visits) for any subject who is unable to tolerate a given dose increase. Subjects will receive this dose for the remainder of the treatment period.

Once a determination of dose escalation, maintenance, or reduction is made, the IWRS will be accessed to obtain an identification number for a kit containing a 2-week supply of study drug to be dispensed to the subject. The subject will remain blinded to dose escalations made during the treatment period; however, the investigator may inform the subject that a dose adjustment is possible if the subject is unable to tolerate a given dose increase.

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

- Instruct subjects of childbearing potential who do not practice total abstinence to continue using contraception (see inclusion criterion #10 in Section 8.1).
- Instruct subjects and parents/legal guardians to notify the investigator by telephone if they experience any AEs and before taking any new concomitant medications.
- Instruct subjects to record the date and time of each dose on the labels provided on the study drug packaging form.

9.6.4. Dose Maintenance Period: Weeks 8, 10, and 12 (-2 to +3 Days for Each Visit)

At Weeks 8, 10, and 12 the following study evaluations and tasks will be performed at the study center:

- Perform a physical examination including weight (Week 12 only).
- Collect vital signs, including orthostatic systolic and diastolic blood pressures, orthostatic pulse rate, respiratory rate, and body temperature.
- Perform 12-lead ECG in triplicate (at least 1 minute apart and within 15 minutes).
- Perform a urine pregnancy test only for female subjects of childbearing potential.
- Collect blood sample for hematology and clinical chemistry.
- Collect urine sample for urinalysis.
- Collect blood sample for serum prolactin.
- Collect PK blood sample for NBI-98854 and metabolite concentrations.
- Administer the YGTSS, including video recording.
- Administer the PUTS.
- Administer the CGI-Tics–Severity scale.
- Administer the CGI-TS–Improvement scale.
- Administer the C-SSRS (Children's Since Last Visit version).
- Administer the CY-BOCS and CDRS-R.
- Administer the ADHD Rating Scale-5.
- Administer the ESRS-A.
- Administer the C&A-GTS-QOL.
- Dispense a 2-week supply of study drug (Weeks 8 and 10 only).
- Perform compliance check by counting the capsules returned.

- AE monitoring.
- Record concomitant medications.

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

- Instruct subjects of childbearing potential who do not practice total abstinence to continue using contraception (see inclusion criterion #10 in Section 8.1).
- Instruct subjects and parents/legal guardians to notify the investigator by telephone if they experience any AEs and before taking any new concomitant medications.
- Instruct subjects to record the date and time of each dose on the labels provided on the study drug packaging form.

9.6.5. Follow-Up Period/Early Termination: Week 14 (-2 to +3 Days)

At Week 14 (or upon early termination) the following study evaluations and tasks will be performed at the study center:

- Perform a physical examination including weight.
- Collect vital signs, including orthostatic systolic and diastolic blood pressures, orthostatic pulse rate, respiratory rate, and body temperature.
- Perform 12-lead ECG in triplicate (at least 1 minute apart and within 15 minutes).
- Perform a urine pregnancy test only for female subjects of childbearing potential.
- Collect blood sample for hematology and clinical chemistry.
- Collect urine sample for urinalysis.
- Collect blood sample for serum prolactin.
- Collect PK blood sample for NBI-98854 and metabolite concentrations.
- Administer the YGTSS, including video recording.
- Administer the PUTS.
- Administer the CGI-Tics–Severity scale.
- Administer the CGI-TS–Improvement scale.
- Administer the C-SSRS (Children's Since Last Visit version).
- Administer the CY-BOCS and CDRS-R.
- Administer the ADHD Rating Scale-5.
- Administer the ESRS-A.
- Administer the C&A-GTS-QOL.
- AE monitoring.
- Record concomitant medications.

9.7. Study Duration

The expected duration of study participation for each subject is approximately 18 weeks, including up to 28 days of screening, a 12-week, double-blind treatment period, and 2 weeks of follow-up, or early termination.

9.8. Prohibitions and Restrictions

9.8.1. 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 14 days before Day 1 (baseline) (unless otherwise stated) until the final study visit (or upon early termination) as described below:

- Antiemetics: Metoclopramide, prochlorperazine, and promethazine.
- Botulinum toxin: Botulinum toxin injections for treatment of TS are prohibited starting 90 days prior to Day 1 (baseline).
- CYP3A4 inducers: Strong inducers of CYP3A4 (eg, phenytoin, phenobarbital, rifabutin, rifampin, primidone, St. John's Wort, carbamazepine).
- CYP3A4 inhibitors: Strong inhibitors of CYP3A4 (eg, itraconazole, ketoconazole, clarithromycin).
- Dopamine agonists and precursors: Dopamine agonists (eg, ropinirole) and precursors (eg, carbidopa/levodopa).
- Dopamine antagonist: Dopamine antagonists (eg, pimozide, haloperidol, aripiprazole, risperidone, clozapine, olanzapine, ziprasidone) are prohibited. Depot neuroleptics are prohibited starting 15 weeks prior to Day 1 (baseline).
- Monoamine oxidase inhibitors (MAOIs): All MAOIs (eg, isocarboxazid, phenelzine, selegiline, tranylcypromine).
- VMAT2 inhibitors: VMAT2 inhibitor medications (eg, tetrabenazine, reserpine), except for study drug.
- As needed use of the following medications: anticholinergics, benzodiazepines, antipsychotics, psychostimulants, mood stabilizers, antidepressants, opiates, and strong CYP2D6 inhibitors.

9.8.2. Dietary Restrictions

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

Grapefruit juice or grapefruit products are prohibited from 7 days before Day 1 until the follow-up visit. Alcohol is prohibited from 48 hours before Day 1 until the follow-up visit.

9.8.3. Other Restrictions

Excessive use of tobacco and other products containing nicotine (including nicotine gum and patches) are prohibited during the study (ie, from 30 days before screening to the follow-up visit or 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.

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

9.9. Withdrawal Criteria

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

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

- If the type, frequency, or severity of any AE becomes unacceptable/intolerable.
- If the subject is unable to tolerate the starting dose or resumption of the previous dose.
- QTcF value >500 msec (cardiologist verified).
- If the subject exhibits suicidal behavior, or suicidal ideation of type 4 (active suicidal ideation with some intent to act, without specific plan) or type 5 (active suicidal ideation with specific plan and intent) based on the C-SSRS.
- 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 9.8.1).
- Is non-compliant with the dosing regimen (<80% dosing compliance) as verified by drug accountability (refer to Section 10.6).

All subjects prematurely discontinuing the study, regardless of cause, must have all early termination assessments performed (see Section 9.6.5).

9.9.1. 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 must have all early termination assessments performed.

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

9.9.2. Sponsor's Termination of Study

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

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

10. STUDY DRUG

10.1. Study Drug Supplies

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

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

The matching placebo capsules are identical in appearance to the NBI-98854 capsules.

All subjects will receive the starting dose of study drug beginning on Day 1. At Weeks 2 and 4, subjects may have their dose increased based on protocol-specified efficacy and safety criteria. Dosing information is provided below.

Subjects <50 kg at baseline:

- Starting dose: 20 mg NBI-98854 (one 20 mg capsule and one placebo capsule) or placebo (2 capsules)
- Week 2: 40 mg NBI-98854 (two 20 mg capsules) or placebo (2 capsules)
- Week 4: 60 mg NBI-98854 (one 20 mg and one 40 mg capsule) or placebo (2 capsules)

Subjects ≥50 kg at baseline:

- Starting dose: 40 mg NBI-98854 (two 20 mg capsules) or placebo (2 capsules)
- Week 2: 60 mg NBI-98854 (one 20 mg and one 40 mg capsule) or placebo (2 capsules)
- Week 4: 80 mg NBI-98854 (two 40 mg capsules) or placebo (2 capsules)

If a subject's optimal dose has already been established at Week 2 (or at Week 4), no further dose escalation will be allowed during the dose optimization period and the subject will continue at that dose until the end of the 12-week treatment period. However, subjects who had a dose escalation may have a dose reduction at any time.

10.2. Study Drug Storage

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

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

10.3. Study Drug Packaging and Labeling

All packaging and labeling operations will be performed per 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. The blistercards will contain capsules of NBI-98854 20 mg or 40 mg; or matching placebo.

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

This study includes a 12-week, double-blind, placebo-controlled treatment period during which the subject, investigator, all study site personnel, and the Sponsor will be blinded to the subject's treatment.

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

10.5. Study Drug Administration

Study drug will be administered qd at bedtime at home under the supervision of the subject's parent/legal guardian and the capsules must be swallowed with at least 4 ounces of water, with or without food, every day for the 12-week treatment period. If a subject forgets or is unable to take the study drug at bedtime, the subject should skip that dose and resume normal dosing 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 center at each study visit for drug accountability and reconciliation by study center personnel. A compliance check will be performed by counting the capsules returned at each study visit.

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

10.7. Study Drug Return

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

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

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

11. ADVERSE EVENTS

All AEs, whether observed by the investigator, reported by the subject, noted from laboratory findings, or identified by other means, will be recorded from the time the subject signed the ICF until the subject's final study visit (Week 14 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.

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

If at any time after the baseline visit (Day 1), the subject's response to the suicidal ideation section of the C-SSRS is worse than the baseline assessment; it will be documented as an AE. All suicidal behaviors will be documented as an AE.

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

The following are not considered AEs:

- Continuous persistent disease/symptom present before drug administration, unless it unexpectedly progresses, or increases in severity following drug administration.
- Recurrence of TS symptoms, unless worsened from baseline.
- Pregnancy.

11.2. Intensity of Adverse Events

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

Table 4: Intensity of Adverse Events

Grade	Intensity
Mild	An 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 5. An AE is deemed associated with the use of the study drug "if there is a reasonable possibility that the drug caused the AE" (otherwise referred to as a suspected adverse reaction). Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the AE (Title 21 CFR 312.32 [a]).

Table 5: Relationship of Adverse Events to Study Drug

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

11.4. Recording Adverse Events

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

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

- 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.

AEs 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 subject has signed the ICF until 30 days after the last dose of study drug.

11.6.1. Definition of a Serious Adverse Event

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

- Death.
- A life-threatening 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, 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 (see inclusion criterion #10 in Section 8.1) until 30 days (females) or 90 days (males) after the last dose of study drug. If at any time between the time the subject signs the ICF and the last study visit a subject believes she is pregnant, the subject will be instructed to stop taking the study medication and return to the study center within 24 hours and undergo a serum pregnancy test to confirm pregnancy.

All confirmed pregnancies, in subjects who received study drug, must be immediately reported to NBI (refer to Section 11.6.3 for contact information), followed by fax or email of the pregnancy form to NBI CDS. A first trimester ultrasound will be required for all confirmed pregnancies. Pregnancies in subjects who received NBI-98854 will be followed until resolution (ie, termination [voluntary or spontaneous] or birth).

12. DOCUMENTATION OF DATA

12.1. Case Report Form

The case report form 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

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

13. STATISTICAL AND ANALYTICAL PLAN

Descriptive and inferential statistical methods will be used to evaluate and summarize the data from this study. The term "descriptive statistics" refers to the number of subjects (n), mean, median, SD, SEM, minimum, and maximum for continuous and ordinal categorical variables; and refers to the number and percentage of subjects for categorical variables. The term "inferential statistics" refers to hypothesis tests which will be performed to assess differences between the NBI-98854 treatment group and the placebo treatment group for selected efficacy variables based on the pooled weight groups (<50 kg and ≥50 kg). Note that descriptive statistics will be presented for the pooled weight groups and for each weight group separately, unless specified otherwise. Only pooled weight groups will be used for inferential statistics.

The primary efficacy endpoint is the change from baseline (Day 1) to the end of Week 12 in the YGTSS TTS as generated by the certified site rater using the Rater Station software. The secondary efficacy endpoints are: change from baseline to the end of Week 12 in CGI-Tics-Severity score, TTS responder status at Week 12 (a responder is defined as having a ≥30% reduction in TTS from baseline), and CGI-TS-Improvement responder status at Week 12 (a responder is defined as having a CGI-TS-Improvement score of either a 1 ["very much improved"] or a 2 ["much improved"]). Exploratory efficacy endpoints include the PUTS total score change from baseline to the end of Week 12, the CGI-TS-Improvement score at the end of Week 12, the C&A-GTS-QOL total score change from baseline to the end of Week 12, as well as changes from baseline to the end of Week 12 for the Global Tic Severity and Impairment scores from the YGTSS. Efficacy data will also be summarized from other timepoints (eg, Weeks 2 through 10).

The primary method of analysis of the YGTSS TTS change from baseline will be a mixed-effect model repeated measures (MMRM) analysis including the scores at Weeks 2, 4, 6, 8, 10, and 12 based on the full analysis set (FAS). Supplemental sensitivity analyses of the primary efficacy endpoint will also be conducted.

Nominal (raw) two-sided p values will be reported for all hypothesis tests, although a procedure to control for multiple comparisons will be applied when interpreting the statistical significance of the results of the analyses of the primary efficacy endpoint and the secondary efficacy endpoints.

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

13.1. Analysis Sets

Three analysis sets will be defined for this study. The safety analysis set will include all subjects who are randomized to a treatment group, take at least one dose of study drug, and have any postbaseline safety data. The FAS will include all subjects who are randomized to a treatment group and who have at least one evaluable TTS change from baseline during the 12-week, double-blind treatment period. The per-protocol (PP) analysis set will include all subjects in the FAS who have a detectable plasma concentration of NBI-98854 at Week 12 (unless randomized to placebo) and no efficacy-related important protocol deviations. Additional analysis set criteria may be specified in the SAP.

13.2. Sample Size

The protocol-specified sample size of 60 subjects per treatment group is based on a power calculation for the YGTSS TTS change from baseline using a two-sample t-test with a two-sided Type I error of 0.05. Power calculations based on this sample size under 3 dropout rate scenarios for 2 hypothesized effect sizes are summarized in the table below. Note that the effect size is defined as the mean difference between the NBI-98854 treatment group and the placebo group divided by the common SD (eg, a mean difference of 8 divided by an SD of 10 yields an effect size of 0.8).

Dropout Rate	Number of Subjects per Treatment Group	Effect Size	Power
0%	60	0.75	98%
		0.85	99%
10%	54	0.75	97%
		0.85	99%
15%	51	0.75	96%
		0.85	98%

Standard deviations reported in the literature for TS studies evaluating changes in the YGTSS TTS (with or without placebo controls) have generally been in the range of 7.5 to 9.5, and in placebo-controlled studies, mean differences between active and placebo arms have been in the range of 5 to 9 (Jankovic et al., 2010; Yoo et al., 2013; ClinicalTrials.gov NCT01727700). The effect sizes of 0.75 and 0.85 mentioned above are representative of effect sizes seen in these published reports.

13.3. Handling of Missing Data

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

13.4. Enrollment and Disposition of Subjects

The summary of subject enrollment and disposition will display the number of subjects who were randomized to each treatment group, who completed the dose optimization period (ie, up to Week 6), who competed the dose maintenance period (ie, up to Week 12), 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.

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

13.5. Demographics and Baseline Characteristics

Demographic data (age, gender, race, and ethnicity) and baseline characteristics (including height, weight, body mass index [BMI], CYP2D6 genotype status, age at TS diagnosis, and baseline values for the YGTSS TTS) will be summarized with descriptive statistics. Medical history will be summarized according to MedDRA System Organ Class (SOC) and Preferred Term (PT).

13.6. Study Drug Dosing and Compliance

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

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

13.7. Pharmacokinetic Data

The plasma concentrations of NBI-98854 and the metabolite NBI-98782 will be summarized with descriptive statistics by visit (Day 1 and Weeks 2, 4, 6, 8, 10, 12, and 14) and dose (last dose received prior to blood sample being drawn). Concentrations below the lower limit of quantification will be set equal to zero for all plasma concentration summaries. These data will be summarized for each weight group separately.

13.8. Efficacy Data

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

13.8.1. Primary Efficacy Endpoint

The primary efficacy endpoint for this study is the change from baseline (Day 1) to the end of Week 12 in the YGTSS TTS (Total Tic Score) as generated by the certified site rater using the Rater Station. Changes from baseline to Weeks 2 through 10 are exploratory efficacy endpoints.

Descriptive statistics will be presented by treatment group for the TTS observed values (ie, the raw data) and changes from baseline at each visit through Week 14. Descriptive statistics will be presented for both the FAS and the PP analysis set.

The primary analysis of the TTS will be an MMRM analysis, which includes the changes from baseline to Weeks 2, 4, 6, 8, 10, and 12, and is based on the FAS. The model will include the baseline TTS as a covariate, and weight group, treatment group, visit, treatment group by visit interaction, and baseline covariate by visit interaction as fixed effects. Subject will be included as a random effect. Study site will not be included in the model, as there are many sites (approximately 55), with most sites anticipated to enroll a small number of subjects.

Treatment group comparisons of the NBI-98854 treatment group vs. placebo at each visit will be performed by constructing linear contrasts (or equivalent programming code) for differences between treatment group least-squares (LS) means. Nominal (raw) two-sided p values for testing the significance of these differences and associated 95% confidence intervals will be reported in summary tables.

A supportive analysis using the MMRM model will be performed with the PP analysis set.

The MMRM analysis will be implemented with the PROC MIXED procedure of SAS®, using the restricted maximum likelihood method, an unstructured within-subject covariance matrix, and denominator degrees of freedom from the Kenward-Roger method. If convergence is not obtained with the unstructured covariance matrix, a Toeplitz covariance structure will be used.

Additional supportive analyses of the TTS change from baseline to the end of Week 12 will be performed using analysis of covariance (ANCOVA) models. The ANCOVA models will include the baseline TTS as a covariate and weight group and treatment group as fixed effects. Response (outcome) variables for the ANCOVAs include the Week 12 TTS score (ie, a complete cases analysis) and the last on-treatment TTS score (ie, a last-observation-carried forward [LOCF] analysis). These analyses will be performed using the FAS.

Additional analyses, including sensitivity analyses to assess the missing at random assumption of the MMRM, will be described in the SAP.

13.8.2. Secondary Efficacy Endpoints

CGI-Tics-Severity

A secondary efficacy endpoint for this study is the change from baseline to the end of Week 12 in CGI-Tics-Severity score. Changes from baseline to Weeks 2 through 10 are exploratory efficacy endpoints.

Descriptive statistics will be presented by treatment group for the CGI-Tics-Severity observed values (ie, the raw data) and changes from baseline at each visit through Week 14. Frequency counts using the response categories will also be presented by visit. Descriptive statistics will be presented for both the FAS and the PP analysis set.

The primary analysis of CGI-Tics-Severity will be an MMRM analysis which includes the changes from baseline to Weeks 2, 4, 6, 8, 10, and 12 and is based on the FAS. The MMRM model will be similar to the model described above for the TTS analysis, with the exception that the covariate in the model will be the baseline value of the CGI-Tics-Severity score. As indicated above for the TTS MMRM analysis, nominal two-sided p values for testing the

significance of treatment group differences and associated 95% confidence intervals will be reported in summary tables; however, interpretation of the p value for the treatment group comparison at Week 12 will be based on a procedure which controls for multiple comparisons (Section 13.8.3).

A supportive analysis of the CGI-Tics-Severity scores will be performed using the MMRM analysis based on the PP analysis set. Additional supportive analyses of the CGI-Tics-Severity scores will be described in the SAP.

Responder Endpoints

The following response statuses at Week 12 will serve as additional secondary endpoints:

- TTS responder: a subject whose TTS value is reduced by at least 30% from baseline.
- CGI-TS-Improvement responder: a subject whose CGI-TS-Improvement score is either a 1 ("very much improved") or a 2 ("much improved").

Response at Weeks 2 through 10 are exploratory efficacy endpoints.

The TTS responder criterion was selected based on a review of studies examining the threshold of tic reduction associated with meaningful clinical response (Storch et al., 2011; Jeon et al., 2013).

Descriptive statistics for each responder definition will be presented by treatment group for the number and percentage of subjects classified as responders at each postbaseline visit.

Analyses comparing the NBI-98854 treatment group to placebo will be performed using the Cochran-Mantel-Haenszel (CMH) procedure, with baseline weight group as a stratification variable.

13.8.3. Procedure to Control for Multiple Comparisons

A fixed-sequence testing procedure will be followed for the primary and secondary efficacy endpoints analyses to control for multiple comparisons (ie, comparing treatment groups for each of the endpoints). The fixed-sequence testing procedure will consist of performing the hypothesis tests in the following prespecified order:

1. Primary endpoint: YGTSS TTS change from baseline to Week 12 (NBI-98854 vs. placebo treatment groups using the FAS).
2. Secondary endpoint: CGI-Tics-Severity change from baseline to Week 12 (NBI-98854 vs. placebo treatment groups using the FAS).
3. Secondary endpoint: TTS response at Week 12 (NBI-98854 vs. placebo treatment groups using the FAS).
4. Secondary endpoint: CGI-TS-Improvement response at Week 12 (NBI-98854 vs. placebo treatment groups using the FAS).

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

13.8.4. Exploratory Efficacy Endpoints

Efficacy endpoints not described in the preceding paragraphs are considered exploratory endpoints. Exploratory efficacy endpoints will include the PUTS total score change from baseline to the end of Week 12, CGI-TS-Improvement score at the end of Week 12, C&A-GTS-QOL total score change from baseline to the end of Week 12, as well as mean changes from baseline to the end of Week 12 for the Global Tic Severity and Impairment scores from the YGTSS. Efficacy data will also be summarized from other timepoints (eg, Weeks 2 through 10). Details regarding the analyses of these endpoints will be provided in the SAP.

13.9. Safety Data

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

Summary tables will be presented including all TEAEs and TEAEs according to maximum intensity.

Additional summaries will be presented for TEAEs leading to study drug dose reductions, premature discontinuations from the study, SAEs, and fatal TEAEs.

Clinical laboratory, vital signs, ECG, C-SSRS, ESRS-A, CY-BOCS, CDRS-R, and ADHD Rating Scale-5 data will be summarized with descriptive statistics. Potentially clinically significant (PCS) values for selected clinical laboratory and vital signs variables will be summarized. Prior and concomitant medications will be summarized according to WHO Drug Anatomical Therapeutic Chemical Classification (ATC) categories.

Any additional planned safety analyses will be described in the SAP.

13.10. Software

Statistical calculations and summaries will be generated using SAS software version 9.4 or later.

13.11. Interim Analysis

An interim analysis is not planned for this study.

14. REGULATORY AND ETHICAL ISSUES

14.1. General Legal References

The study will be carried out according to the provision of the US CFR, the US FDA, Health Canada, 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 (originals should be kept by the investigator in the investigator's regulatory document binder):

- Signed copy of the approved protocol.
- Investigator's Brochure acknowledgement page.
- Completed and signed statement of investigator (Form FDA 1572 and/or Clinical Trial Site Information Form – as applicable).
- Curriculum vitae and current medical license of the investigator and subinvestigators.
- Financial disclosure information as required.
- Letter of approval from the IRB for 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

All parents or legal guardians will provide informed consent with signed and witnessed pediatric assent 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. 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, Health Canada Guidelines, and according to national law. Quality assurance audits may be performed at the discretion of NBI.

14.8. Record Retention

Federal regulations require that records of drug disposition, 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

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

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

16. REFERENCES

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