

STATISTICAL ANALYSIS PLAN

PHASE 3

VERSION 1.0

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STUDY DRUG:

NBI-98854

PROTOCOL NUMBER:

NBI-98854-1402

STUDY TITLE:

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

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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification
BARS	Barnes Akathisia Rating Scale
BLQ	Below the limit of quantification
BPRS	Brief Psychiatric Rating Scale
CDSS	Calgary Depression Scale for Schizophrenia
CGI-TD	Clinical Global Impression of Change –Tardive Dyskinesia
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP2D6	Cytochrome P450 2D6
ECG	Electrocardiogram
eCRF	Electronic case report form
EPS, EPSE	Extrapyramidal symptoms or side effects
ET	Early termination
FDA	[United States] Food and Drug Administration
GGT	Gamma-glutamyl transferase
HBsAg	Hepatitis B surface antigen
HCV-Ab	Hepatitis C antibody
HIV-Ab	Human immunodeficiency virus antibody
ICF	Informed Consent Form
IPD	Important protocol deviation
ITT	Intent-to-treat
LS	Least squares
MADRS	Montgomery-Asberg Depression Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
n, N	Sample size (number of subjects)
NBI	Neurocrine Biosciences, Inc.
NDA	New Drug Application

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Abbreviation	Term
PANSS	Positive and Negative Syndrome Scale
PCS	Potentially clinically significant
PGIC	Patient Global Impression of Change
PK	Pharmacokinetic(s)
PP	Per-protocol
PT	Preferred term
qd	Once daily
QTcF	Fridericia's correction of QT interval
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Simpson-Angus Scale
	statistical software
SD	Standard deviation
SEM	Standard error of the mean
SIGMA	Structured Interview Guide for the Montgomery-Asberg Depression Rating Scale
SOC	System organ class
TEAE	Treatment-emergent adverse event
TD	Tardive dyskinesia
TDIS	Tardive Dyskinesia Impact Scale
UBACC	University of California, San Diego Brief Assessment of Capacity to Consent
UDS	Urine drug screen
WHO	World Health Organization
YMRS	Young Mania Rating Scale

LIST OF DEFINITIONS

The following definitions are developed for the purpose of statistical analysis and data tabulation.

Adverse Event	<p>An adverse event (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, electrocardiograms (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.</p> <p>Adverse events include, but are not limited to: (1) a worsening or change in nature, severity, or frequency of conditions present at the start of the study; (2) subject deterioration due to primary illness; (3) intercurrent illness; and (4) drug interaction</p>
Descriptive Statistics	<p>Number of subjects, mean, median, standard deviation, standard error of the mean, minimum and maximum for continuous measurements; number and percentage of subjects in each level of a categorical measurement. (Note: additional descriptive statistics may be calculated for certain variables if warranted.)</p>
Life-Threatening	<p>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.</p>
Serious Adverse Event	<p>A serious adverse event (SAE) is any AE that results in any of the following outcomes:</p> <ul style="list-style-type: none">• Death;• A life-threatening adverse event;• Inpatient hospitalization or prolongation of existing 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 above.

Treatment-Emergent Adverse Event A Treatment-Emergent Adverse Event (TEAE) is any reaction, side effect, or other untoward event, regardless of relationship to study drug, that is newly reported or considered a worsening or change in nature, severity, or frequency of conditions present at the start of the study which occurs any time after first dose of study drug.

1. INTRODUCTION

This statistical analysis plan (SAP) provides a detailed description of the tables, figures, and listings that will be prepared to summarize the data from the Phase 3 study described in Neurocrine Biosciences, Inc. (NBI) Protocol NBI-98854-1402.

2. STUDY OBJECTIVES

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

3. STUDY DESIGN

3.1. Study Design Overview

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

All subjects must sign an informed consent form (ICF) prior to the conduct of any study related procedures, including washout of medications disallowed in the study. Before subjects can provide informed consent, the investigator (or designee) must determine whether the subject has the capacity to provide consent for study participation using the University of California, San Diego Brief Assessment of Capacity to Consent (UBACC). Only subjects who are deemed to have the capacity to provide consent may sign the ICF. After providing informed consent, the subjects will be screened for eligibility for up to 6 weeks prior to Day -1 (baseline visit) (Week -6 to Day -1).

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

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

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

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

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

3.2. Efficacy, Blood Sampling, and Safety Assessments for All Subjects

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

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

The PGIC will be used to evaluate the change in TD symptoms since initiation of study drug dosing, and will be completed by the subjects during the treatment period (Weeks 4, 8, 12, 24, 36, and 48) and at the follow-up visit (Week 52) or early termination.

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

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

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

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

3.3. Additional Safety Assessments for Subjects with Schizophrenia or Schizoaffective Disorder

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

3.4. Additional Safety Assessments for Subjects with Mood Disorder

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

4. STUDY ASSESSMENT SCHEDULES

The schedules of assessments for subjects with schizophrenia or schizoaffective disorder and subjects with mood disorder are shown in [Table 1](#) and [Table 2](#), respectively.

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

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

Abbreviations and footnotes appear on the next page.

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

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

Table 2: Schedule of Assessments for Subjects with Mood Disorder

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

Abbreviations and footnotes appear on the next page.

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

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

5. STATISTICAL ANALYSES

All analyses described in this plan are considered *a priori* analyses in that they have been defined prior to locking the study database. Analyses defined subsequent to locking the database will be considered *post hoc* analyses and will be applied as exploratory methodology. Any *post hoc* analyses will be clearly identified in the clinical study report.

5.1. General Statistical Procedures

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

Unless stated otherwise, each table of descriptive statistics and associated figures will summarize data according to the following “treatment groups”:

- NBI-98854 40 mg (subjects who are not titrated to the 80 mg dose at Week 4)
- NBI-98854 80 mg (subjects who are titrated to the 80 mg dose at Week 4 and remain on that dose)
- NBI-98854 80/40 mg (subjects who are titrated to the 80 mg dose at Week 4 and subsequently have a dose reduction to 40 mg at any time in the study)
- All subjects (this may also be referred to as “overall” in treatment groups specifications below)

Note that subjects who discontinue from the study prior to the Week 4 titration visit will be included in the NBI-98854 40 mg treatment group.

5.2. Sample Size

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

5.3. Data Locks and Analyses

Three analyses of this study will be performed, each of which will involve locking study data for a defined subset of the overall study database for purposes of statistical analysis. The study data locking process will be carried out by the sponsor’s Clinical Data Management department in accordance with company standard operating procedures (SOPs).

5.3.1. Data Lock and Analysis 1

The first data lock will be performed prior to an analysis of the study data that will be included in a New Drug Application (NDA) to be submitted to the US Food and Drug Administration (FDA) for the use of NBI-98854 for the treatment of TD. Data included in this analysis will be locked for any subject who has completed or early terminated from the study at the time of data cutoff. For subjects who are still participating in the study, all data for visits that occurred by the time of data cutoff (with the exception of ongoing adverse events, concomitant medications, and study drug dosing and accountability) will also be locked prior to performing the analysis.

5.3.2. Data Lock and Analysis 2

The second data lock/analysis will occur at the time the safety update is prepared for the NDA referenced above in Section 5.3.1. The specific data to be locked for Analysis 2 will be determined at the time of Analysis 2, which will be performed by an external vendor.

5.3.3. Data Lock and Analysis 3

The third and final data lock/analysis will occur when all subjects have completed the study. All study data will be locked prior to this analysis. Analysis 3 will include all of the data reported during the study, and the results of this analysis will be presented in the final clinical study report.

5.4. Pooling of Sites

With exception of the summary of subject enrollment by site, study sites will be pooled in all tables and graphs, since the majority of sites in this study are expected to enroll fewer than five subjects.

5.5. Handling of Early Termination Visit Data

An early termination (ET) visit occurs when a subject discontinues from the study prior to completing the scheduled Week 52 visit. According to the study protocol, subjects who discontinue early from the study are to be asked to schedule their ET visit to occur approximately 4 weeks after their last dose of study drug; however, study experience to date indicates that only a small number of subjects are returning for a follow-up visit after their last dose, and the timing of this visit is variable. The ET visit mapping algorithm described below applies to only those subjects whose ET visit does not occur at a follow-up visit after the subjects have stopped dosing with study drug (ie, have not had study drug kits dispensed), with the exception of the Week 52 visit (which occurs 4 weeks after a subject has completed the treatment period).

For the purpose of data summarization, a visit window will be applied to account for ET visits. An ET visit will be mapped to Week 4 if it occurs within 7 days prior to and 6 days after the expected study day of the Week 4 visit. For scheduled study visits at Weeks 8 through 48, an ET visit will be mapped to the next scheduled study visit if it occurs within 14 days prior to and 13 days after the expected study day of the visit. Early termination visit data which are not mapped to a scheduled visit will be displayed in applicable by-subject data listings but not included in by-visit summaries.

Table 3 displays the allowable study day range for each scheduled visit for ET visit mapping purposes.

Table 3: Allowable Study Day Range for Early Termination Visit Mapping

Scheduled Visit	Target Study Day	Time Interval (Study Day Range)
Week 4	28	21-34
Week 8	56	42-69
Week 12	84	70-97
Week 16	112	98-125
Week 20	140	126-153

Scheduled Visit	Target Study Day	Time Interval (Study Day Range)
Week 24	168	154-181
Week 28	196	182-209
Week 32	224	210-237
Week 36	252	238-265
Week 40	280	266-293
Week 44	308	294-321
Week 48	336	322-349
Week 52	364	350+

5.6. Handling of Missing Data

Missing values for outcome measures will not be replaced with imputed values except as noted above for the ET visit data mapped to scheduled visits for data summary purposes.

Derived scale total scores (eg, the YMRS score), which are calculated as the sum of the scores of the individual scale items, will be set equal to missing if any of the individual scale item scores are missing.

Special rules for handling missing and incomplete dates are described below.

5.6.1. Missing and incomplete dates

Missing and incomplete (“partial”) dates for AEs and concomitant medications will be imputed only for the purpose of estimating the time of the event or medication usage in relationship to study treatment periods (eg, NBI-98854 treatment period vs. follow-up period); however, all data listings will display the original dates as reported on the eCRF.

The imputation rules for AE start dates are as follows:

- If the date is completely missing, the date will be imputed as the date of the first dose of study drug following dispensing of study drug on Day -1;
- If only the day component is missing from the date, the date will be imputed as the date of the first dose of study drug if the date is in the same month and year as the first dose of study drug; otherwise, the missing day component will be imputed as the first day of the month;
- If both the day and month components are missing from the date, the date will be imputed as the date of the first dose of study drug if the date is in the same year as the first dose; otherwise, the missing components will be imputed as 01 January;
- If any of the above imputations result in a start date that is later than an existing complete (not imputed) end date for the event, the start date will be set equal to the end date.

The imputation rules for concomitant medication start dates are as follows:

- If the date is completely missing, the date will be imputed as 01 January in the year of the subject’s screening vital signs assessment;

- If only the day component is missing from the date, the date will be imputed as the date of the first dose of study drug if the date is in the same month and year as the first dose of study drug; otherwise, the missing day component will be imputed as the first day of the month;
- If both the day and month components are missing from the date, the date will be imputed as the date of the first dose of study drug if the date is in the same year as the first dose; otherwise, the missing components will be imputed as 01 January;
- If any of the above imputations result in a start date which is later than an existing complete (not imputed) medication stop date, the start date will be set equal to the stop date.

5.7. Coding Dictionary

Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 12.0). Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary.

5.8. Analysis Sets

The safety analysis set will be the single analysis set defined for this study. The safety analysis set will include all subjects who are enrolled into the study and dispensed study drug, with the following two exclusions: (a) subjects who withdraw from the study and return all previously dispensed study drug with all doses present, and (b) subjects who have no postbaseline data collected.

A summary of the number and percentage of subjects included in (and excluded from, as applicable) the safety analysis set will be provided for each treatment group. The number and percentage of subjects excluded from the safety analysis set by reason for exclusion will also be provided.

Summaries of subject enrollment and disposition, enrollment by study site, and analysis set inclusion/exclusion status will include all enrolled subjects. All other summaries will be based on the safety analysis set.

Individual subject listings of all available data will be provided for all enrolled subjects.

5.9. Subject Enrollment and Disposition

The summary of subject enrollment and disposition will display, by treatment group and overall (ie, “all subjects”), the number and percentage of subjects who enrolled in the study, completed the study through at least Week 4, completed the study through at least Week 8, completed the study through at least Week 48 (end of the treatment period), and completed the study through Week 52 (the final study visit). The table will also summarize, for each of the study timepoints listed in the previous sentence, the number and percentage of subjects who did not complete the study according to the reason for study discontinuation.

Programming considerations related to the determination of subject completion status for each interim timepoint specified in the above paragraph (eg, Week 8) are as follows: subjects who have a visit date in the study database for their scheduled Week XX visit (XX refers to any one

of the specified timepoints) or who have an ET visit which is mapped to the Week XX visit according to the algorithm described in [Section 5.55](#) will be considered to have completed the study through this timepoint for the purpose of this summary.

A separate summary of enrollment by study site will be presented. This summary will display the number of subjects enrolled at each site, by treatment group and for all subjects, and will be presented by disease category (schizophrenia/schizoaffective disorder or mood disorder) as well as with both disease categories combined.

5.10. Important Protocol Deviations

Important protocol deviations (IPDs) are protocol deviations that might significantly affect the completeness, accuracy and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being. An assessment of IPDs will be performed by a committee composed of NBI Clinical Development project team members. Important protocol deviations may include, but are not limited to the following:

- Failure to obtain informed consent from the subject prior to performing any study procedures
- Deviations from key inclusion/exclusion criteria
- Use of prohibited concomitant medications
- Error in drug dispensing which results in a subject not receiving intended treatment
- Significant deviation from protocol-specified dosing regimen

The number and percentage of subjects with IPDs will be summarized by deviation category, treatment group, and for all subjects.

5.11. Demographics

Demographic data (age, gender, race, and ethnicity) will be summarized with descriptive statistics by treatment group and overall.

5.12. Baseline Subject Characteristics

The following baseline subject characteristics will be summarized with descriptive statistics by treatment group and overall:

- Weight (at screening; in units of pounds and kilograms)
- Height
- Body mass index
- CYP2D6 metabolizer genotype
- Disease category (schizophrenia/schizoaffective disorder or mood disorder)
- Age at diagnosis of schizophrenia/schizoaffective disorder
- Age at diagnosis of mood disorder
- Age at diagnosis of tardive dyskinesia
- BPRS total score
- AIMS dyskinesia total score at Day -1 (from central AIMS video raters)

5.13. Medical History

Medical history will be summarized in frequency tables (number and percentage of subjects) by MedDRA System Organ Class (SOC) and Preferred Term (PT) for each treatment group and overall.

5.14. Study Drug Dosing

5.14.1. Number of Doses Taken

The estimated number of doses of study drug taken by each subject between consecutive scheduled visits will be summarized with descriptive statistics for each treatment group and overall by visit. The estimated total number of doses taken by each subject through Week 48 will be summarized also.

The estimated number of doses taken by each subject between visits will be calculated based on the difference between the number of capsules dispensed at the first visit and the number of capsules returned at the subsequent visit (note that the number of 80 mg doses is equal to the number of capsules of study drug divided by two and the number of 40 mg doses is equal to the number of capsules of study drug). If an early termination visit occurs between scheduled visits, the early termination visit data will be used in the calculation. If a subject fails to return the study drug kit dispensed at the previous visit, it will be assumed that the number of doses taken by the subject is equal to the number of days between visits (inclusive of the day of the second visit). If a subject is lost to follow-up between visits, they will be excluded from the summary statistics for all visits occurring after the last visit at which they were present.

The estimated number of doses taken by a subject across all study visits is calculated as the sum of the number of doses taken between each pair of consecutive visits throughout the subject's participation in the study (through Week 48 or the subject's early termination visit if applicable).

5.14.2. Dosing Compliance

Estimated study drug dosing compliance is calculated as the ratio of the estimated number of doses taken (calculated as described above in [Section 5.14.1](#)) to the expected number of doses that should have been taken, and is expressed as a percentage. A subject is classified as being dose compliant if their calculated value is 80% or greater. The number and percentage of subjects who were dose compliant will be summarized by treatment group and overall by visit as well as across all visits through Week 48.

The expected number of doses that should have been taken by a subject between or across visits is defined as the expected number of days the subject should have dosed with study drug during the interval of interest, based on the duration of the subject's study participation during the interval (which may be shorter, for example, if the subject withdraws from the study).

For dosing compliance between successive scheduled study visits, the expected number of days of dosing is calculated as the difference between the visit date of the second of the two visits and the study drug kit dispense date at the first of the two visits. Note that the expected number of days of dosing cannot exceed the number of doses dispensed. If an early termination visit occurs between scheduled visits, the early termination visit date will be used in the calculation. If a subject fails to return the study drug kit(s) dispensed at the previous visit, the expected number

of days of dosing will be set equal to the number of days between visits (inclusive of the day of the second visit). If a subject is lost to follow-up between scheduled visits, they will be excluded from the compliance calculations for all visits occurring after the last visit at which they were present.

The dosing compliance calculation for the overall treatment period will follow the logic described above, with the expected number of days of dosing being equal to the difference between the Week 48 (or early termination) visit date and the Study Day -1 drug kit dispense date. The estimated number of doses taken by a subject across all visits is calculated as the sum of the number of doses taken between each pair of consecutive visits during the treatment period. If a subject is lost to follow-up prior to Week 48, their dosing compliance will be based on the last study visit at which they were present.

5.15. Dose Titration at Week 4

The number and percentage of subjects whose dose is (a) increased from 40 mg to 80 mg at Week 4 vs. (b) maintained at 40 mg, will be summarized.

5.16. Dose Reductions after Week 4

The dose reduction summary will present the number of subjects with a dose reduction (from 80 mg to 40 mg) at each visit from Week 8 through Week 44. Dose reductions at unscheduled visits will be included in the summary for the next scheduled visit (eg, dose reductions between Week 8 and Week 12 will be counted in the Week 12 results). If any subjects have a dose reduction after Week 44, a line for Week 48 will be added to the table with a clarifying footnote.

In addition, the table will include the total number of subjects with a dose reduction at any time during the study.

5.17. Pharmacokinetic Data

The plasma concentrations of NBI-98854 and its active metabolite NBI-98782 will be summarized with descriptive statistics by visit (Weeks 4, 8, 12, 24, 36, 48, and 52) and the most recent NBI-98854 dose received by a subject prior to that visit. Note that the Week 52 dose level will reflect the last dose received prior to the Week 48 visit. These summaries will also be generated separately for CYP2D6 poor metabolizers vs. non-poor metabolizers. Concentrations below the lower limit of quantification (BLQ) will be set equal to zero for all plasma concentration summaries. The lower limits of quantification are as follows: (a) NBI-98854: 1.00 ng/mL and (b) NBI-98782: 0.100 ng/mL.

The following additional descriptive statistics will be included in the plasma concentration summary tables: (a) the number of plasma concentration values greater than or equal to the lower limit of quantification, (b) the geometric mean, and (c) the geometric coefficient of variation (%).

The descriptive statistics presented for the plasma concentration data will be rounded to three significant figures in all summary tables.

Plasma concentrations of each PK analyte will be summarized graphically with box plots by NBI-98854 dose level at each visit.

5.18. Efficacy Data

5.18.1. Efficacy Variables

The primary efficacy variable for this study is the AIMS dyskinesia total score based on the central AIMS video rater assessments. Secondary efficacy variables include the CGI-TD, PGIC, TDIS, and AMBMTD. The AIMS dyskinesia total score based on the AIMS scoring performed at the study sites by the investigators (or designees) is considered as an exploratory variable.

Descriptive statistics will be presented for each efficacy variable, with the exception of the AMBMTD, which will be presented only in a data listing. For the AIMS data, both central AIMS video rater and investigator assessments will be summarized.

5.18.2. AIMS

5.18.2.1. Individual AIMS Items Descriptive Statistics

Scores for the individual AIMS items 1 through 7 (as scored by both the central AIMS video raters and investigators) will be summarized with descriptive statistics by treatment group and visit. Scores for AIMS items 8 through 10 (which are scored only by the investigators) will be summarized also.

5.18.2.2. Individual AIMS Dyskinesia Total Score Descriptive Statistics

The AIMS dyskinesia total score is defined as the sum of the scores of AIMS items 1 through 7. If any of the seven items has a missing value, the total score for that subject/visit will be set equal to missing.

Descriptive statistics will be presented by treatment group for the AIMS dyskinesia total score observed values (ie, the raw data) at each visit (for the investigator data: screening, Day -1, and Weeks 4, 8, 12, 24, 36, 48, and 52; for the central AIMS video rater data: Day -1, Week 8, and Week 52) and for the changes from baseline (Day -1) at each postbaseline visit. Two-sided 95% confidence intervals (CIs) will be included in the descriptive statistics for changes from baseline.

Descriptive statistics (including CIs for changes from baseline) will be presented by disease category (schizophrenia/schizoaffective disorder or mood disorder) for the central AIMS video rater data only.

5.18.2.3. AIMS Dyskinesia Total Score Graphs

Mean (\pm SEM) values of the central AIMS video rater AIMS dyskinesia total score at each visit at which the AIMS is scored (from Day -1, Week 8, and Week 52) will be summarized in line graphs by treatment group. A similar graph will be presented for the mean changes from baseline (Day -1).

5.18.2.4. AIMS Responder Analysis

An AIMS responder is defined, on a per-visit basis, as a subject whose AIMS dyskinesia total score is reduced by at least 50% from baseline (Day -1) at the specified postbaseline visit. The percentage of subjects classified as AIMS responders based on the central AIMS video rater data will be summarized for each treatment group at Weeks 8 and 52.

A bar graph displaying the percentage of subjects classified as AIMS responders at Weeks 8 and 52 will be presented by treatment group.

5.18.3. CGI-TD

5.18.3.1. CGI-TD Scores

Each of the seven CGI-TD response categories will be assigned a numerical score as follows:

- Very much improved = 1
- Much improved = 2
- Minimally improved = 3
- No change = 4
- Minimally worse = 5
- Much worse = 6
- Very much worse = 7

5.18.3.2. CGI-TD Descriptive Statistics

Descriptive statistics (including both categorical variable statistics [using response categories] and continuous variable statistics [using numerical scores]) will be presented by treatment group for the CGI-TD data at Weeks 4, 8, 12, 24, 36, 48, and 52.

Descriptive statistics for CGI-TD scores and response categories will be presented also by disease category (schizophrenia/schizoaffective disorder or mood disorder).

5.18.3.3. CGI-TD Score Graphs

Mean (\pm SEM) values of the CGI-TD score at Weeks 4, 8, 12, 24, 36, 48, and 52 will be summarized in line graphs by treatment group.

5.18.3.4. CGI-TD Responder Analysis

Two definitions of a CGI-TD responder will be used for this study. For the first definition (“CGI-TD Responder 1”), a subject is classified as a responder if their CGI-TD score is either a “1” (“very much improved”) or a “2” (“much improved”). For the second definition (“CGI-TD Responder 2”), a subject is classified as a responder if their CGI-TD score is either a “1”, a “2”, or a “3” (“minimally improved”). Similar to the AIMS responder outcome measure described above, a CGI-TD responder is defined on a per-visit basis, based on the data reported at that visit.

The number and percentage of subjects classified as CGI-TD responders will be summarized for each treatment group at Weeks 4, 8, 12, 24, 36, 48, and 52. Each responder definition will be summarized separately.

Descriptive statistics for the CGI-TD responder analysis will also be presented by disease category (schizophrenia/schizoaffective disorder or mood disorder).

Bar graphs displaying the percentage of subjects classified as CGI-TD responders (using both definitions) will be presented by treatment group at Weeks 4, 8, 12, 24, 36, 48, and 52.

5.18.4. PGIC

5.18.4.1. PGIC Scores

Each of the seven PGIC response categories will be assigned a numerical score as follows:

- Very much improved = 1
- Much improved = 2
- Minimally improved = 3
- No change = 4
- Minimally worse = 5
- Much worse = 6
- Very much worse = 7

5.18.4.2. PGIC Descriptive Statistics

Descriptive statistics (including both categorical variable statistics [using response categories] and continuous variable statistics [using numerical scores]) will be presented by treatment group for the PGIC data at Weeks 4, 8, 12, 24, 36, 48, and 52.

Descriptive statistics for the PGIC scores and response categories will also be presented by disease category (schizophrenia/schizoaffective disorder or mood disorder).

5.18.4.3. PGIC Score Graphs

Mean (\pm SEM) values of the PGIC scores at Weeks 4, 8, 12, 24, 36, 48, and 52 will be summarized in line graphs by treatment group.

5.18.4.4. PGIC Responder Analysis

Two definitions of a PGIC responder will be used for this study. For the first definition (“PGIC Responder 1”), a subject is classified as a responder if their PGIC score is either a “1” (“very much improved”) or a “2” (“much improved”). For the second definition (“PGIC Responder 2”), a subject is classified as a responder if their PGIC score is either a “1”, a “2”, or a “3” (“minimally improved”). Similar to the AIMS responder outcome measure described above, a PGIC responder is defined on a per-visit basis, based on the data reported at that visit.

The number and percentage of subjects classified as PGIC responders will be summarized for each treatment group at Weeks 4, 8, 12, 24, 36, 48, and 52. Each responder definition will be summarized separately.

Descriptive statistics for the PGIC responder analysis will also be presented by disease category (schizophrenia/schizoaffective disorder or mood disorder).

Bar graphs displaying the percentage of subjects classified as PGIC responders (using both definitions) will be presented by treatment group at Weeks 4, 8, 12, 24, 36, 48, and 52.

5.18.5. TDIS Total Score

The TDIS total score is defined as the sum of the scores of TDIS items 1 through 11. If any of the 11 items have a missing value, the total score for that subject/visit will be set equal to missing.

5.18.5.1. TDIS Total Score Descriptive Statistics

Descriptive statistics will be presented by treatment group for the TDIS total score observed values (ie, the raw data) at screening, Day -1, and Weeks 4, 8, 12, 24, 36, 48, and 52, and for the changes from baseline (Day -1) at each postbaseline visit. Two-sided 95% confidence intervals (CIs) will be included in the descriptive statistics for changes from baseline.

Descriptive statistics will also be presented by disease category (schizophrenia/schizoaffective disorder or mood disorder).

5.18.5.2. TDIS Total Score Graphs

Mean (\pm SEM) values of the TDIS total score at Day -1 and Weeks 4, 8, 12, 24, 36, 48, and 52 will be summarized in line graphs by treatment group. A similar graph will be presented for the mean changes from baseline (Day -1).

5.18.6. Assessment of Most Bothersome Movement

The assessment of AMBMTD will be presented in a data listing.

5.19. Safety Data

5.19.1. Adverse Events

5.19.1.1. Treatment-Emergent Adverse Event Frequency Tables

TEAEs, categorized by MedDRA (Version 12.0) SOC and PT, will be summarized with frequency tables. Unless stated otherwise, the frequency tables will include the number of events reported, and the number and percentage of unique subjects experiencing each event one or more times during the study interval summarized in the table. A description of each table is provided below. Note that AEs with an onset date during screening (“pretreatment AEs”) will be presented only in a data listing.

NBI-98854 Treatment Period through Week 4 Visit

TEAEs with an onset date during the first four weeks of the NBI-98854 treatment period (after Day -1 through Week 4) will be summarized separately from TEAEs that occur after the Week 4 visit, as all subjects receive the same dose of 40 mg during the first 4 weeks of treatment. These tables will therefore not be “by treatment” and will summarize data for all subjects as a single group.

Tables will be presented which include all TEAES, only TEAEs considered to be possibly or definitely related to study drug, and TEAEs categorized according to the maximum intensity reported for a given subject.

These TEAEs will also be presented by PT only (ie, not by SOC), with PTs sorted according to decreasing frequency of subjects reporting each event.

NBI-98854 Treatment Period after Week 4 Visit

TEAEs with an onset date during the NBI-98854 treatment period after Week 4 through Week 48 will be summarized by treatment group. This table will include a separate column for all subjects.

Similar tables will be presented including only TEAEs considered to be possibly or definitely related to study drug and categorizing TEAEs according to the maximum intensity reported for a given subject.

These TEAEs will also be presented by PT only (ie, not by SOC), with PTs sorted according to decreasing frequency of subjects reporting each event based on the “all subjects” column.

Posttreatment Period

TEAEs with an onset date during the posttreatment period (after Week 48 through Week 52) will be summarized using the approach described above for the NBI-98854 treatment period after the Week 4 visit.

NBI-98854 Treatment after Week 4 Visit Period and Posttreatment Period Combined

TEAEs with an onset date at any time during the study after the Week 4 visit will be summarized using the approach described above for the NBI-98854 treatment period after the Week 4 visit.

5.19.1.2. Adverse Event Overall Summaries

Overall summary tables will be provided which summarize the number and percentage of subjects with any TEAE, any treatment-related TEAE (ie, possibly or definitely related per electronic case report form [eCRF]), any severe TEAE, any TEAE leading to study discontinuation, any serious TEAE, and any TEAE resulting in death. An overall summary table will be presented for each of the study intervals described above in Section 5.19.1.1.

These tables will summarize data by treatment group (with the exception of the summary for the first 4 weeks of treatment) and will also include an “all subjects” column.

5.19.1.3. Adverse Event Time to Onset and Duration

Descriptive statistics for TEAE time to onset and duration will be presented by treatment group (and for “all subjects”) for selected TEAEs associated with study drug pharmacology and for other common TEAEs. TEAEs reported during the NBI-98854 treatment period at the Week 4 visit or earlier will be summarized separately from TEAEs reported after the Week 4 visit, similar to the TEAE frequency tables described in Section 5.19.1.1. Examples of PTs that may be included are as follows (note that additional PTs may be included and that PTs may be combined for summary purposes upon review of the study data):

- Fatigue
- Somnolence
- Insomnia
- Anxiety
- Sedation

Time to onset will be calculated for the first subject report of a given TEAE PT and summarized with standard descriptive statistics in units of days. Duration (in units of days) will be calculated as the TEAE end date minus the TEAE start date +1 for each subject TEAE. If a subject reports the same TEAE more than once, the duration will be calculated as the average of all of the durations for that TEAE PT. If a TEAE is ongoing at the time a subject either completes the study or has an early termination visit, the TEAE end date will be set equal to the subject’s final

study visit date. If a TEAE is missing an end date due to the interim nature of the data at the time of the first data lock and analysis (Section 5.3.1), the duration for that TEAE will be considered to be a missing value and will not be included in any statistical summaries. Duration will be summarized with standard descriptive statistics.

5.19.1.4. Adverse Events Resulting in a Study Drug Dose Reduction

A summary of TEAEs resulting in a study drug dose reduction (from 80 mg to 40 mg) will be presented. This summary table will display the PTs for the TEAEs resulting in a dose reduction, with the PTs sorted in order of decreasing frequency (based on number of subjects). The first line of the table will display the total number of subjects with a dose reduction.

A listing of TEAEs resulting in a study drug dose reduction will be included in the study report. This listing will include subject, study day of the dose reduction, and both the PT and reported term for all TEAEs that resulted in the dose reduction (note that the specific PTs resulting in a dose reduction are determined from the AE eCRF “action taken with study drug” field).

5.19.1.5. Adverse Events Resulting in Premature Study Discontinuation

Three summary tables of TEAEs resulting in premature study discontinuation will be presented. Tables will be presented for the following study periods:

- NBI-98854 treatment period after Day -1 through Week 4
- NBI-98854 treatment period after Week 4 through Week 48
- Posttreatment period (after Week 48 through Week 52)

These summary tables will include both the SOC and PT, with data summarized by treatment group (for study intervals after Week 4) and overall (all subjects). Note that the onset date of the TEAE(s) resulting in study discontinuation will be the basis for determining the study period assignment.

A listing of TEAEs resulting in premature study discontinuation at any time prior to the final scheduled visit at Week 52 will be presented in the study report following the tables described above. The listing will include subject, treatment group, study period when the TEAE which resulted in study discontinuation occurred (NBI-98854 treatment period after Day -1 through Week 4, NBI-98854 treatment period after Week 4 through Week 48, or posttreatment period), study day of the discontinuation, and both the PT and reported (verbatim) term for all TEAEs that resulted in the premature study discontinuation (note that this is determined from the AE eCRF “action taken” field).

5.19.1.6. Deaths and Other Serious Adverse Events

The frequency of SAEs will be summarized in tables using the approach described above in [Section 5.19.1.5](#). The table formats (which include both the SOC and PT) for the SAE tables will match those used for the TEAE discontinuation tables. Deaths will be presented in a listing only.

Listings of SAEs and deaths will be presented in the study report following the tables described in the previous paragraph. These listings will include subject, treatment group, study period when the death or SAE occurred, study day of the death or SAE, and all other AE-specific information reported on the AE eCRF.

5.19.1.7. Adverse Event Graphs

Horizontal bar graphs (known as “swimmer’s” plots) will be presented for the TEAE PTs listed above in Section 5.19.1.3 (fatigue, somnolence, insomnia, anxiety, and sedation). A separate graph will be generated for each of these PTs. The graph for each PT will display horizontal bars for each subject who reported that PT at least once during their participation in the study. The start and end dates of each individual TEAE report (where available) will be indicated on each bar, and a special symbol will be plotted at the end of the bar if the subject discontinued the study early due to the TEAE. The length of the bar will represent the total duration of the subject’s participation in the study (the x-axis will be displayed in units of weeks). Treatment will be color-coded for each bar.

5.19.2. C-SSRS

The C-SSRS data will be presented in the following summaries:

- Screening/lifetime assessment by treatment group and for all subjects
- Screening/past 3 months assessment by treatment group and for all subjects
- Baseline (Day -1) assessment by treatment group and for all subjects
- NBI-98854 treatment period assessments (Day 1 through Week 48) by treatment group and for all subjects
- Posttreatment period assessments (after Week 48) by treatment group and for all subjects
- All postbaseline assessments (Day 1 through Week 52) by treatment group and for all subjects

Each summary will display the number and percentage of subjects who report “Yes” to specific C-SSRS items or categories of items (a category is assigned a “Yes” value if a “Yes” is reported for any item in the category). These C-SSRS items and categories are as follows:

- Suicidal Ideation Items
 - (1) Wish to be dead
 - (2) Non-specific active suicidal thoughts
 - (3) Active suicidal ideation with any methods (not plan) without intent to act
 - (4) Active suicidal ideation with some intent to act, without specific plan
 - (5) Active suicidal ideation with specific plan and intent
- Suicidal Ideation Category: Any of items (1) through (5)
- Suicidal Behavior Items
 - (6) Preparatory acts or behavior
 - (7) Aborted attempt
 - (8) Interrupted attempt
 - (9) Non-fatal suicide attempt
 - (10) Completed suicide

- Suicidal Behavior Category: Any of items (6) through (10)
- Suicidal Ideation or Behavior Category: Any of items (1) through (10)

For each subject, the C-SSRS responses for all assessments (including both scheduled and unscheduled visits) during a given study interval (eg, the NBI-98854 treatment period) will be evaluated, and a “Yes” response for any assessment will be considered as a “Yes” for the subject for that study interval.

In addition to the summaries described above, shift tables comparing postbaseline suicidal ideation scores to baseline (Day -1) scores will be presented for the NBI-98854 treatment and posttreatment periods combined (ie, including all assessments after baseline). The shift table scores are defined as the following:

- 0=No suicidal ideation
- 1=Wish to be dead
- 2=Non-specific active suicidal thoughts
- 3=Active suicidal ideation with any methods (not plan) without intent to act
- 4=Active suicidal ideation with some intent to act, without specific plan
- 5=Active suicidal ideation with specific plan and intent

The shift tables will display the number and percentage of subjects within each cell of a 6 x 6 table for each treatment group and for all subjects, with the rows representing the baseline score and the columns representing the maximum score recorded during the study period of interest (at all visits, including unscheduled visits). Subjects missing either a baseline score or all postbaseline scores will not be summarized.

A summary listing of individual subject data will be presented for the C-SSRS data and will be provided in the study report following the tables described above. This summary will list subjects with a positive response for suicidal ideation, suicidal behavior, or self-injurious behavior without suicidal intent at any time during after Day -1. The listing will be in the form of a table, with each row representing a subject visit (including treatment group and study day for that visit), and a column for each suicidal ideation item (1 – 5), each suicidal behavior item (6 – 10), and a final column for self-injurious behavior without suicidal intent. The cells of the table will be populated with “Y” or “N,” representing either a positive or negative response, respectively, for each item in the table (ie, for each column of the table).

5.19.3. Barnes Akathisia Rating Scale

The BARS total score is calculated as the sum of Items 1 through 3 of the BARS. The BARS total score for a subject at a specific visit will be set equal to missing if any of these items have a missing value. Both the BARS total score and the BARS global score (Item 4) will be summarized with descriptive statistics for observed values and changes from baseline (Day -1) by treatment group and for all subjects at Day -1 and Weeks 4, 12, 24, 36, 48, and 52.

The BARS total score and global score mean values (\pm SEM) at each of the visits listed in the previous paragraph will be summarized by treatment group in line graphs.

5.19.4. Simpson-Angus Scale

The SAS global score is calculated as the mean of the scores of the 10 individual items comprising the scale (note that the mean value can be calculated even if one or more of the individual items is missing). The SAS global score observed values and changes from baseline (Day -1, or screening if the Day -1 value is missing) will be summarized with descriptive statistics by treatment group and for all subjects at screening, Day -1, and Weeks 4, 12, 24, 36, 48, and 52.

The SAS global score mean values (\pm SEM) at each visit listed in the previous paragraph (with the exception of screening) will be summarized by treatment group in line graphs.

5.19.5. Positive and Negative Symptoms Scale (Subjects with Schizophrenia or Schizoaffective Disorder)

The total score will be calculated for each of the three sections of the PANSS (positive symptoms, negative symptoms, and general psychopathology) as the sum of the individual item scores. In addition, the composite scale will be calculated as the difference between the positive symptoms total score and the negative symptoms total score. A total score will be set equal to missing if any of the individual items used in calculating the score has a missing value.

Each of the total score variables and the composite scale (both observed values and changes from baseline [Day -1]) will be summarized with descriptive statistics by treatment group and for all subjects at Day -1 and Weeks 4, 12, 24, 36, 48, and 52.

Mean values (\pm SEM) for each of the PANSS section total scores and the composite scale at each visit listed in the previous paragraph will be summarized by treatment group in line graphs.

5.19.6. Calgary Depression Scale for Schizophrenia (Subjects with Schizophrenia or Schizoaffective Disorder)

The CDSS total score is calculated as the sum of the 9 items that comprise the CDSS scale. If any individual item has a missing value for a subject visit, the total score will be set equal to missing for that subject visit.

The CDSS total score observed values and changes from baseline (Day -1, or screening if the Day -1 value is missing) will be summarized with descriptive statistics by treatment group and for all subjects at screening, Day -1, and Weeks 4, 12, 24, 36, 48, and 52.

The CDSS total score mean values (\pm SEM) at each visit listed in the previous paragraph will be summarized by treatment group in line graphs.

5.19.7. Young Mania Rating Scale (Subjects with Mood Disorders)

The YMRS total score is calculated as the sum of the scores of the 11 individual items comprising the scale. The YMRS total score at a subject visit will be set equal to missing if any of the 11 individual items have a missing value at that subject visit.

The YMRS total score observed values and changes from baseline (Day -1, or screening if the Day -1 value is missing) will be summarized with descriptive statistics by treatment group and for all subjects at screening, Day -1, and Weeks 4, 12, 24, 36, 48, and 52.

The YMRS total score mean values (\pm SEM) at each visit listed in the previous paragraph will be summarized by treatment group in line graphs.

5.19.8. Montgomery-Asberg Depression Rating Scale (Subjects with Mood Disorders)

The MADRS total score is calculated as the sum of the scores of the 10 individual items comprising the scale. The MADRS total score for a subject visit will be set equal to missing if any of the 10 individual items have a missing value at that subject visit.

The MADRS total score observed values and changes from baseline (Day -1, or screening if the Day -1 value is missing) will be summarized with descriptive statistics by treatment group and for all subjects at screening, Day -1, and Weeks 4, 12, 24, 36, 48, and 52.

The MADRS total score mean values (\pm SEM) at each visit listed in the previous paragraph will be summarized by treatment group in line graphs.

5.19.9. Physical Examination and Weight

Clinically significant physical examination findings will be presented by subject and visit in a listing. The listing will include subject, treatment group, visit at which the finding was reported, study day of the visit, and the clinically significant finding.

Body weight, which is measured during the physical examination, will be summarized in units of kilograms with descriptive statistics (both observed values and changes from baseline [Day -1, or screening if the Day -1 value is missing]), by treatment group and for all subjects at screening, Day -1, and Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52.

5.19.10. Vital Signs

The vital signs data, including orthostatic blood pressures and heart rate (calculated as standing value minus supine value), will be summarized with descriptive statistics by treatment group and for all subjects at screening, Day -1, and Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52. Both observed values and changes from baseline (Day -1, or screening if the Day -1 value is missing) will be summarized.

Sponsor-defined potentially clinically significant (PCS) values for systolic blood pressure, diastolic blood pressure, and heart rate will be summarized by treatment group and for all subjects in frequency tables for each of the following treatment periods:

- NBI-98854 treatment period (after Day -1 through Week 48)
- Posttreatment period (after Week 48 through Week 52)

The number and percentage of subjects with one or more PCS values during a given treatment period will be presented in the summary tables. Note that data collected at both scheduled and unscheduled study visits will be included in this assessment. The criteria for identifying PCS values are provided in Table 4.

Table 4: Potentially Clinically Significant Criteria for Selected Vital Signs

Variable Name	PCS – Low if:		PCS – High if:	
	Observed Value is:	Decrease from Baseline is:	Observed Value is:	Increase from Baseline is:
Systolic Blood Pressure	<90 mmHg	≥20 mmHg	>180 mmHg	≥20 mmHg
Diastolic Blood Pressure	<50 mmHg	≥10 mmHg	>105 mmHg	≥15 mmHg
Heart Rate	<50 bpm	≥15 bpm	>120 bpm	≥15 bpm

Note that both supine and standing values of blood pressures and heart rate will be included in the identification and summary of PCS values.

A listing of all subjects with a PCS value during either of the two specified treatment periods will be presented following the summary tables in the study report. This listing will include vital signs data at all study visits for each subject with one or more PCS values. The listing will include subject, treatment group, visit, study day of visit, systolic blood pressure (supine and standing), diastolic blood pressure (supine and standing), and heart rate (supine and standing). Values that meet the PCS criteria will be flagged with an asterisk in the listing.

5.19.11. Electrocardiogram

The triplicate values of the quantitative ECG variables (heart rate, PR interval, QRS duration, QT interval, and Fridericia's correction of QT interval [QTcF]) measured at each visit will be averaged for the purpose of analysis. For the overall assessment categorical variable (the investigator's assessment of the ECG as Normal, Abnormal not Clinically Significant, or Abnormal Clinically Significant), which is also reported in triplicate, the value that represents the greatest degree of abnormality will be used in all summary tables.

The ECG variables will be summarized with descriptive statistics (frequency tables for the overall assessment categorical variable) by treatment group and for all subjects at screening, Day -1, and Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52. Both observed values and changes from baseline (Day -1, or screening if the Day -1 value is missing) will be summarized (for the overall categorical assessment, only observed values will be summarized).

Categorical summaries will be presented for the QT and QTcF interval data for the NBI-98854 treatment period and for the posttreatment period. For each of these treatment periods, a subject's highest reported value (including assessments at both scheduled and unscheduled study visits) will be used to determine in which category(s) the subject will be counted.

Two categorical summaries will be presented for the QT and QTcF intervals (each interval will be summarized separately). For the first summary, the number and percentage of subjects in each treatment group (and for all subjects) whose highest reported QT/QTcF value in a given treatment period meets the following thresholds will be summarized:

- Greater than 450 msec
- Greater than 480 msec

- Greater than 500 msec

The second categorical summary will display the number and percentage of subjects in each treatment group (and for all subjects) whose largest QT/QTcF increase from their baseline value in a given treatment period meets the following thresholds:

- Greater than 30 msec
- Greater than 60 msec

5.19.12. Clinical Laboratory Data

The hematology, clinical chemistry, and prolactin data will be summarized with descriptive statistics by treatment group and for all subjects. The hematology and clinical chemistry data will be summarized at screening, Day -1, and Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52. Both observed values and changes from baseline (Day -1, or screening if the Day -1 value is missing) will be summarized. The prolactin data will be summarized at Day -1 and Weeks 4, 12, 24, 36, 48, and 52 (both observed values and changes from Day -1).

The prolactin data will be summarized for each gender separately, in addition to the summaries described above.

Shift tables will be presented for selected clinical laboratory variables based on the reference range-based categories of “Low,” “Normal,” or “High.” A clinical laboratory variable value will be assigned to one of these three categories according to the reference ranges provided by the central clinical laboratory.

Each shift table will have three rows and three columns, with rows reflecting the reference range category at baseline, and columns reflecting the reference range category at one of two postbaseline visits: Week 8 or Week 48. Subjects with missing data for a clinical laboratory variable at either baseline or at the specified postbaseline visit will not be included in tables for that variable. The shift tables will be presented for each treatment group and for all subjects.

Shift tables will be displayed for the following clinical laboratory variables: AST, alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), total bilirubin, creatine kinase, creatinine, BUN, prolactin, hemoglobin A1c, white blood cell count, absolute neutrophil count, hemoglobin, and platelet count.

Summaries of sponsor-defined PCS values will be presented for the following clinical laboratory variables: ALT, AST, creatinine kinase, GGT, total bilirubin, white blood cell count, neutrophil count, creatinine, and BUN. Similar to the PCS summaries for the vital signs data, these data will be summarized by treatment group and for all subjects in frequency tables for each of the two following treatment periods:

- NBI-98854 treatment period (after Day -1 through Week 48)
- Posttreatment period (after Week 48 through Week 52)

The number and percentage of subjects with one or more PCS values during a given treatment period will be presented in the summary tables. Note that data collected at both scheduled and unscheduled study visits will be included in this assessment. The criteria for identifying PCS values are provided in [Table 5](#).

Table 5: Potential Clinically Significant Criteria for Selected Clinical Laboratory Variables

Variable	PCS Threshold
ALT	>3 x ULN (upper limit of normal)
AST	>3 x ULN
Creatine kinase	>5 x ULN
GGT	>3 x ULN
Total bilirubin	>1.5 x ULN
White blood cell count	$\leq 2.8 \times 1000/\mu\text{L}$
Absolute Neutrophil count	$<1.5 \times 1000/\mu\text{L}$
Creatinine	>1.5 x Day -1 value or > 1.5 x ULN
BUN	>30 mg/dL ($> 10.71 \text{ mmol/L}$)

A listing of all subjects with any PCS value in any of the two specified treatment periods will be presented following the summary tables in the study report. This listing will include the values of the clinical laboratory variables in Table 5 at all study visits for each subject with one or more PCS values. The listing will include subject, treatment group, visit, study day of visit, and all laboratory results for the analytes with a PCS value. Values that meet the PCS criteria will be flagged with an asterisk in the listing.

Scatter plots of selected variables will be created which display Week 8 values vs. baseline values. Each plot will include a 45 degree (“y=x”) reference line. The plots will be generated by treatment group and for all subjects for ALT, AST, creatine kinase, GGT, total bilirubin, and prolactin.

Similar scatter plots of Week 48 values vs. baseline values will be presented by treatment group and for all subjects.

The clinical laboratory data listings will include associated normal/reference ranges (if provided). In addition, values outside the normal range will be flagged as “L” if below the lower limit of normal and as “H” if above the upper limit of normal. There will also be a flag for clinical significance based on the investigator’s assessment of out-of-range values. The urinalysis data will be presented in data listings only.

Repeat clinical laboratory samples may be collected at any time during this study due to either missing or abnormal results. The general rule of thumb for summarizing these data is to include the original sample results in summary tables and graphs. One exception to this rule is when there are missing results from the original samples at screening – in this situation, the results of a repeat screening sample will be substituted for the missing results in summary tables and graphs. All sample results (original and repeat) will be included in data listings.

5.19.13. Prior and Concomitant Medications

Prior medications (taken within 30 days of screening or within the previous two years for indications of schizophrenia/schizoaffective disorder, mood disorder, extrapyramidal symptoms or side effects [EPSE], and TD) and concomitant medications will be summarized by WHO Drug Anatomical Therapeutic Chemical Classification (ATC) Level 3 category (or Level 2 if there is not an applicable Level 3 category) and preferred name.

Medications will be assigned to one or more study periods based on the medication start and stop dates relative to the study drug dosing. For example, medications that were started and stopped prior to the date of the first dose of study drug will be assigned to the prestudy/screening period only, while medications started prior to the first dose of study drug and either stopped during the NBI-98854 treatment period or indicated as “ongoing” will be assigned to both the prestudy/screening and NBI-98854 treatment periods. A given medication can therefore be assigned to one or more study periods in the tabular summaries, depending on its start and end dates.

The number and percentage of subjects using medications in each WHO Drug ATC category (Level 3/preferred name) will be summarized by treatment group and for all subjects for each study period as described in the next paragraph. A subject may take the same medication more than once or multiple medications for a subject may be classified under the same ATC level or preferred name. A subject is counted only once for each level of medication classification within a summary.

The summary of medications taken prestudy or during screening will be presented by treatment group and for all subjects. Medications taken during the NBI-98854 treatment or posttreatment periods will also be summarized by treatment group and for all subjects.

5.20. Additional Data Presentations

5.20.1. Inclusion and Exclusion Criteria

Inclusion and exclusion criteria confirmation results will be presented in a data listing by subject.

5.20.2. Serology Test Results

Serology assessments (ie, Human immunodeficiency virus antibody [HIV-Ab], Hepatitis B surface antigen [HBsAg], and Hepatitis C antibody [HCV-Ab]) collected at screening will be reviewed at the study site to ensure the entry criteria are met. The HBsAg and HCV-Ab test results will be presented in a listing by subject. The results of the HIV-Ab test will not be listed, but will be kept on file at the study site.

5.20.3. Pregnancy Test Results

Serum and urine pregnancy test results will be presented in a listing by subject.

5.20.4. Urine Drug Screen and Alcohol Breath Test

Urine drug screen and alcohol breath test results will be presented in a listing by subject.

5.20.5. Plasma Sampling Timepoints for Exploratory Biomarker Assessments

The plasma sampling timepoints for exploratory biomarker assessments will be presented in a listing by subject.

6. DEVIATIONS FROM PROTOCOL PLANNED ANALYSIS

The SAP includes a number of additional summaries not described in the study protocol. In addition the definition of the safety analysis set is further refined in the SAP, and the treatment groups described in the SAP replace the “dose level” treatment categories mentioned in the study protocol.

7. PERFORMANCE QUALIFICATION OF [REDACTED]

The analysis and summary of data from this study will be performed using [REDACTED] [REDACTED]. All [REDACTED] programs used in the production of statistical analyses, tables, listings, and figures described in this SAP will undergo performance qualification (verification that the program produces the intended output) in accordance with department standard operating procedures. The performance qualification may include independent programming and/or peer review of the [REDACTED] log files. In addition, tables, figures, listings, and statistical analysis output will be independently reviewed for completeness and accuracy.

8. REFERENCES

None.