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Note; This document was translated into English from Japanese original version.

A Double-Blind, Randomized, Multicenter, Placebo-Controlled, Parallel, Fixed-Dose Study to Evaluate the Efficacy and Safety of MT-5199 for the Treatment in Patients with Tardive Dyskinesia (J-KINECT)

Protocol

Sponsor

Mitsubishi Tanabe Pharma Corporation

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Confidentiality

This study protocol contains information provided limitedly to individuals directly involved in the relevant clinical study. Information in this protocol may not be published or disclosed to any third party without prior written consent of Mitsubishi Tanabe Pharma Corporation.

This clinical study should be conducted in compliance with the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices, the Ministerial Ordinance on Good Clinical Practice (GCP), applicable laws and regulations, and the protocol.

Table of Contents

LIST OF ABBREVIATIONS

Abbreviation	Description of abbreviations
AIMS	Abnormal Involuntary Movement Scale
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
BARS	Barnes Akathisia Rating Scale
BMI	Body mass index
CDSS	Calgary Depression Scale for Schizophrenics
CGI-TD	Clinical Global Impression of Change – Tardive Dyskinesia
C_{max}	Maximum plasma concentration
CMC	Chemistry, Manufacturing and Control
CPK	Creatine phosphokinase
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	Cytochrome P450
DNA	Deoxyribonucleic acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
EDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EQ-5D-5L	EuroQoL 5-dimension 5- level
GCP	Good Clinical Practice
γ-GTP	γ-glutamyltranspeptidase
HBs	Hepatitis B surface
HCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HDL	High density lipoprotein
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ITT	Intent-to-Treat
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LS Mean	Least squares Mean
MADRS	Montgomery-Åsberg Depression Rating Scale
MedDRA	Medical dictionary for regulatory activities
MMRM	Mixed Models for Repeated Measures
MMSE	Mini mental state examination
NOAEL	No-observed-adverse-effect level
PANSS	Positive and Negative Syndrome Scale
PP	Per-Protocol
PT	Preferred term

Abbreviation	Description of abbreviations
QOL	Quality of life
QTcF	Fridericia's correction of QT interval
SAE	Serious adverse event
SAS	Simpson-Angus extrapyramidal side effects scale
SD	Standard Deviation
SE	Standard Error
$t_{1/2}$	Terminal elimination half-life
ULN	Upper limit of normal
VMAT2	Vesicular monoamine transporter 2
WHO	World Health Organization
YMRS	Young Mania Rating Scale

DEFINITIONS OF TERMS

Term	Description of terms
Study period	The study period is the period from the time when informed consent is obtained until the end of post-study examination (or, if follow-up is performed, until the end of the follow-up or the time when the follow-up is discontinued).

Summary of Study Protocol

1. Study Title

A Double-Blind, Randomized, Multicenter, Placebo-Controlled, Parallel, Fixed-Dose Study to Evaluate the Efficacy and Safety of MT-5199 for the Treatment in Patients with Tardive Dyskinesia (J-KINECT)

2. Study Objectives

The objective of this study is to evaluate the efficacy and safety of MT-5199 (40 mg or 80 mg) administered once daily in patients with clinical diagnoses of schizophrenia or schizoaffective disorder, or bipolar disorder or depressive disorder and TD.

- The superiority of MT-5199 (40 mg and 80 mg) over placebo will be tested by using the change from baseline in the AIMS total score (Items 1 to 7; central assessment [redacted]) at Week 6 as an index.
- The safety of 6-week treatment with MT-5199 (40 mg/day or 80 mg/day), as well as the efficacy and safety during a 42-week extension period, will be evaluated.

3. Study Subjects

3.1 Study Subjects

Patients with clinical diagnoses of schizophrenia or schizoaffective disorder, or bipolar disorder or depressive disorder and TD

3.2 Inclusion Criteria

Patients who satisfy all of the following inclusion criteria, have an adequate understanding of the study, and have given written consent to participate in the study will be enrolled.

(1) Men and women aged 20 to 85 years at the time of informed consent obtainment

(2) Patients diagnosed with schizophrenia, schizoaffective disorder, bipolar disorder, or depressive disorder according to the diagnostic criteria of DSM-5 at least 3 months before informed consent obtainment

(3) Patients diagnosed with TD (DSM-5 code: 333.85) according to the diagnostic criteria of DSM-5 prior to informed consent obtainment

(4) Patients judged to be with moderate or severe TD (AIMS Item 8, severity of abnormal movement overall) on central AIMS assessment [redacted]

(5) Patients in whom the dosage regimen of maintenance therapy drugs for schizophrenia, schizoaffective disorder, bipolar disorder, or depressive disorder, and psychotropic drugs used for extrapyramidal symptoms, etc. have not been changed since at least 30 days before the start of the pre-treatment observation period (or, for benzodiazepines, at least 14 days before the start of the pre-treatment observation period)

(6) (If maintenance therapy drugs are not used for schizophrenia, schizoaffective disorder, bipolar disorder, or depressive disorder) Patients whose psychiatric symptoms are stable as judged by the investigator (or subinvestigator) during the pre-treatment observation period

(7) Patients with a BMI $\geq$ 17.0 and $<$ 35.0 at screening (BMI calculation formula: body weight (kg)/height $(m)^2$, rounded to second decimal place)

3.3 Exclusion Criteria

Patients who fall under any of the following exclusion criteria will be excluded from the study.

- All subjects

(1) Patients with active, clinically significant, unstable cerebrovascular disease, hepatic disease, renal disease, endocrine disease, cardiovascular disease, gastrointestinal disease, respiratory disease, metabolic disease, etc. during the pre-treatment observation period (refer to Grade 3 in [redacted] "Criteria for Classification of the Seriousness of Adverse Reactions to Pharmaceuticals, etc.")

(2) Patients diagnosed with dementia according to the diagnostic criteria of DSM-5 during the pre-treatment observation period

(3) Patients judged to be with prominent abnormal involuntary movements, such as coexisting dystonia, akathisia, or parkinsonism, and TD which cannot be properly evaluated on central AIMS assessment based [redacted]

(4) Patients with an SAS score of 3 or greater at baseline in two or more items (except Items 8 and 10)

(5) Patients with substance-related disorder (except tobacco- or caffeine-related disorder) according to the diagnostic criteria of DSM-5 within 3 months before initial randomization

(6) Patients at high risk of suicidal or self-injurious behavior as judged by the investigator (or subinvestigator), and patients with suicidal attempts or suicidal ideation corresponding to Item 4 or 5 on C-SSRS assessment at baseline (within 3 months before evaluation)

(7) Patients with a history of neuroleptic malignant syndrome within 3 years before initial randomization

(8) Patients with a history of long QT syndrome or tachyarrhythmia within 3 years before initial randomization

(9) Patients with a QTcF ≥450 msec (men) or ≥470 msec (women) on a standard 12-lead electrocardiogram (ECG) at screening

(10) Patients with laboratory abnormalities at screening (However, those who fall under "3) only (γ-GTP ≥3×ULN)" may be enrolled, subject to the approval of the sponsor's medical expert).

1) Serum creatinine >1.5×ULN

2) ALT or AST ≥2.5×ULN

3) γ-GTP ≥3×ULN

4) Total bilirubin >1.5 mg/dL

5) Hemoglobin <10 g/dL

6) White blood cell count <3,000/mm^3

7) Platelet count <100,000/mm^3

(11) Patients with a history of malignant tumor within 3 years before initial randomization. However, complete excision of basal cell carcinoma or squamous cell carcinoma of the skin is excluded.

(12) Patients who tested positive for HBs antigen, HCV antibody, or HIV antibody in the Infection and virus tests at screening (However, HCV antibody-positive patients may be enrolled only if HCV RNA testing is negative).

(13) Patients who have received another investigational drug within 6 months before initial randomization

(14) Patients with previous treatment with deep brain stimulation within 3 years before initial randomization

(15) Patients with a history of surgery known to affect digestive tract absorption of drugs

(16) Patients with a history of drug allergy or previous tetrabenazine administration (However, patients with a history of drug allergy may be enrolled, subject to the approval of the sponsor's medical expert).

(17) Patients who do not agree to use appropriate contraception from the time of informed consent obtainment until 28 days after the completion (discontinuation) of study treatment

(18) Female patients who are pregnant, breastfeeding, or possibly pregnant

(19) Other patients who are ineligible for this study as judged by the investigator (or subinvestigator).

- Subjects with schizophrenia or schizoaffective disorder

(20) Patients with a total JCDSS score of 10 or higher at baseline

(21) Patients with a total PANSS score of 70 or higher at baseline

- Subjects with bipolar disorder or depressive disorder

(22) Patients hospitalized for treatment of bipolar disorder or major depressive disorder within 6 months before initial randomization

(23) Patients with mood episodes (manic symptoms and depressive symptoms) within 3 months before initial randomization

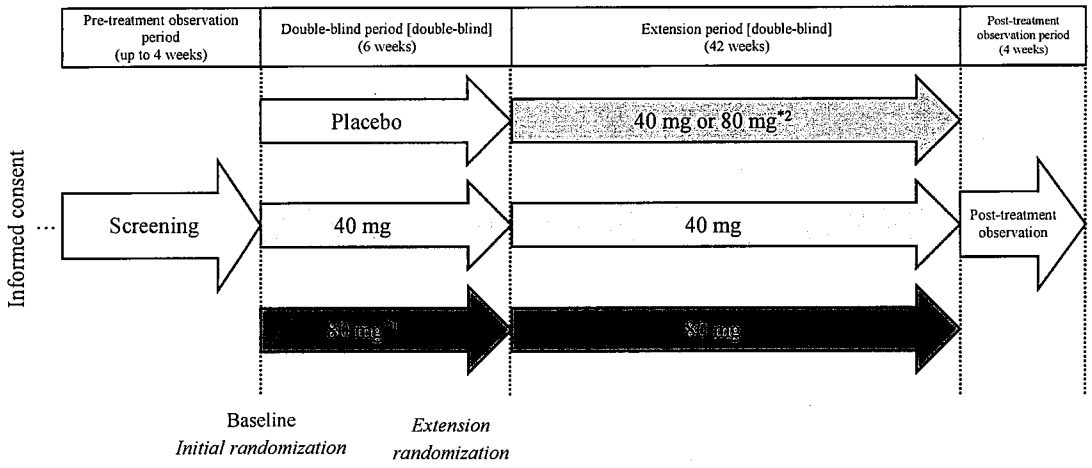
(24) Patients with a history of rapid cycling (more than four episodes in a year) or ultra-rapid cycling (more than four episodes in a month)

(25) Patients with a total MADRS-J score of more than 13 at baseline

(26) Patients with a total YMRS score of more than 10 at baseline

4. Study Design

This study is a Phase II/III, randomized, double-blind, placebo-controlled, multicenter, parallel-group, fixed-dose study. The study period consists of a pre-treatment observation period of up to 4 weeks, a double-blind period of 6 weeks (placebo-controlled study treatment period), a 42-week extension period (MT-5199 administration period), and a 4-week post-treatment observation period.



*1: Subjects randomized to the MT-5199 80 mg group in the double-blind period will receive MT-5199 at a dose of 40 mg/day on Day 1 to Day 7 of the double-blind period.
*2: Subjects initially randomized to the placebo group in the double-blind period and then to the MT-5199 80 mg group in the extension period will receive MT-5199 at a dose of 40 mg/day on Day 1 to Day 7 of the extension period.

Figure 1 Overview of the Study Design

Subjects deemed eligible based on the inclusion and exclusion criteria will be randomized to the placebo group, MT-5199 40 mg group, or MT-5199 80 mg group at a ratio of 1:1:1 on the day of randomization (Initial randomization) and treated with the study drug for 6 weeks.

In the randomization prior to the start of the extension period (Extension randomization), subjects who were randomized to the placebo group in the initial randomization will be randomized to either the MT-5199 40 mg group or the MT-5199 80 mg group (at a randomization ratio of 1:1), and subjects who were randomized to either of the MT-5199 groups in the initial randomization will be randomized to the same dose group.

Subjects randomized to the MT-5199 80 mg group in the double-blind period will receive MT-5199 at a dose of 40 mg/day on Day 1 to Day 7 of the double-blind period. Subjects randomized to the placebo group in the double-blind period and then to the MT-5199 80 mg group in the extension period will receive MT-5199 at a dose of 40 mg/day on Day 1 to Day 7 of the extension period.

5. Study Drugs, Dosage, Administration, and Treatment Period

5.1 Study Drugs

(1) Investigational product

MT-5199 40 mg capsule

- A capsule containing 40 mg free base equivalent of MT-5199 ditosylate salt

(2) Control drug

MT-5199 placebo capsule

- A capsule that is indistinguishable in appearance from the investigational product but does not contain MT-5199 ditosylate salt

5.2 Dosage, Administration, and Treatment Period

Two capsules of the randomized study drug will be orally administered once a day every morning for up to 48 weeks. However, the time of administration may be changed only if the investigator (or subinvestigator) judges that it is unavoidable for the treatment of adverse events, etc. (such a change will become effective on or after the following day of the decision). The time of administration may be changed only once per subject (e.g., if morning administration is changed to evening administration, a change from evening administration to morning administration or whatever is not allowed thereafter). The study drug may be taken with or without a meal, and should be taken at the same time of day whenever possible throughout the treatment period.

In subjects randomized to the MT-5199 80 mg group in the double-blind period, the dose should be increased in a blinded manner (40 mg/day in Week 1 and 80 mg/day from Week 2 onwards in the double-blind period). In subjects randomized to the placebo group in the double-blind period and then to the MT-5199 80 mg group in the extension period, the dose should be increased in a blinded manner (40 mg/day in Week 1 and 80 mg/day from Week 2 onwards in the extension period).

The number of capsules to be taken at a time may be changed from two to one if a serious adverse event, important adverse event (see Section 11.2 "Important Adverse Events"), Parkinson-like event, clinically significant laboratory abnormality, etc. are observed after the start of the extension period, and the investigator (or subinvestigator) deems it necessary to ensure the safety of the subjects (however, such a change is not allowed in the double-blind period). The number of capsules to be taken at a time may be changed only once per subject. Also, the number of capsules to be taken at a time may not be changed from one to two. If the sign, symptom, or disease concerned does not tend to improve even after the change, the study treatment should be discontinued. To maintain the study blind, subjects in the placebo group or the MT-5199 40 mg group who undergo such a change will continue receiving the original dose, while those in the MT-5199 80 mg group will receive the study drug at a dose

of 40 mg after the change.

(1) Placebo group

Two MT-5199 placebo capsules

(2) 40 mg group

One MT-5199 40 mg capsule and one MT-5199 placebo capsule

(3) 80 mg group

Two MT-5199 40 mg capsules

Subjects randomized to the MT-5199 80 mg group in the double-blind period will receive MT-5199 at a dose of 40 mg/day on Day 1 to Day 7 of the double-blind period. Subjects randomized to the placebo group in the double-blind period and then to the MT-5199 80 mg group in the extension period will receive MT-5199 at a dose of 40 mg/day on Day 1 to Day 7 of the extension period (once-daily administration of one MT-5199 40 mg capsule and one MT-5199 placebo capsule).

6. Concomitant Medications and Therapies

6.1 Treatment of Schizophrenia, Schizoaffective Disorder, Bipolar Disorder, or Depressive Disorder, and Extrapyramidal Symptoms, etc.

Treatment of schizophrenia, schizoaffective disorder, bipolar disorder, or depressive disorder, and extrapyramidal symptoms, etc. should be provided as specified below in each period.

(1) From 30 days before the start of the pre-treatment observation period to the start of the pre-treatment observation period

1) The dosage regimen of maintenance therapy drugs for schizophrenia, schizoaffective disorder, bipolar disorder, or depressive disorder, and psychotropic drugs used for extrapyramidal symptoms, etc. (including antiparkinsonian drugs but excluding drugs used as sleeping drugs) should be kept unchanged from at least 30 days before the start of the pre-treatment observation period (or, for benzodiazepines, at least 14 days before the start of the pre-treatment observation period).

2) Benzodiazepines should be used only as maintenance therapy drugs for schizophrenia, schizoaffective disorder, bipolar disorder, or depressive disorder, or as sleeping drugs, and should not be used for other purposes.

3) Among sleeping drugs, the dosage regimen of benzodiazepines should be kept unchanged from at least 14 days before the start of the pre-treatment observation period. Administration of sleeping drugs other than benzodiazepines, including those classified as ultra-short-acting drugs, may be newly started. AIMS

examination/assessment should be performed following an interval of at least 8 hours after the use of a sleeping drug, regardless of the type of the sleeping drug used.

(2) From the start of the pre-treatment observation period to the end of the double-blind period

1) Administration of maintenance therapy drugs for schizophrenia, schizoaffective disorder, bipolar disorder, or depressive disorder, and psychotropic drugs used for extrapyramidal symptoms, etc. (including antiparkinsonian drugs but excluding drugs used as sleeping drugs) should be continued without any change in the dosage regimen even after the start of the pre-treatment observation period, and these drugs should not be either discontinued or newly started.

2) Benzodiazepines should be used only as maintenance therapy drugs for schizophrenia, schizoaffective disorder, bipolar disorder, or depressive disorder, or as sleeping drugs, and should not be used for other purposes.

3) Among sleeping drugs, administration of benzodiazepines should be continued without any change in the dosage regimen even after the start of the pre-treatment observation period, and these drugs should not be either discontinued or newly started. Administration of sleeping drugs other than benzodiazepines, including those classified as ultra-short-acting drugs, may be newly started. AIMS examination/assessment should be performed following an interval of at least 8 hours after the use of a sleeping drug, regardless of the type of the sleeping drug used.

(3) From the start of the extension period to the end of the post-treatment observation period

1) The prescription of maintenance therapy drugs for schizophrenia, schizoaffective disorder, bipolar disorder, or depressive disorder, and psychotropic drugs used for extrapyramidal symptoms, etc. (including antiparkinsonian drugs but excluding drugs used as sleeping drugs) may be modified (including discontinuation and new administration) only if the investigator (or subinvestigator) judges that it is unavoidable for the treatment of adverse events, etc.

2) The prescription of benzodiazepines may be modified (including discontinuation and new administration) only if the investigator (or subinvestigator) judges that it is unavoidable for the treatment of adverse events, etc.

3) The prescription of sleeping drugs may be modified (including discontinuation and new administration) only if the investigator (or subinvestigator) judges that it is unavoidable for the treatment of adverse events, etc. If a sleeping drug is used, however, AIMS examination/assessment should be performed following an interval of at least 8 hours after the use of the sleeping drug.

6.2 Prohibited Concomitant Medications and Therapies [redacted]

(1) From 90 days before the start of the pre-treatment observation period to the end of the double-blind period

- Botulinum toxin injection

(2) From 30 days before the start of the pre-treatment observation period to the end of the double-blind period (or, for 8) and 10) below, until the end of the extension period)

1) New administration of maintenance therapy drugs for schizophrenia, schizoaffective disorder, bipolar disorder, or depressive disorder, and psychotropic drugs used for extrapyramidal symptoms, etc. (including antiparkinsonian drugs)

- Administration of drugs that have been used without any change in the dosage regimen for at least 30 days before the start of the pre-treatment observation period may be continued.

- Administration of sleeping drugs other than benzodiazepines, including those classified as ultra-short-acting drugs, may be newly started. However, AIMS examination/assessment should be performed following an interval of at least 8 hours after the use of a sleeping drug.

2) New administration of benzodiazepines

- Administration of maintenance therapy drugs for schizophrenia, schizoaffective disorder, bipolar disorder, or depressive disorder, or sleeping drugs that have been used without any change in the dosage regimen from at least 14 days before the start of the pre-treatment observation period may be continued. If a benzodiazepine is used as a sleeping drug, AIMS examination/assessment should be performed following an interval of at least 8 hours after the use of the benzodiazepine.

3) Drugs and foods with potent CYP3A4 inhibitory or inducing action

4) Drugs with potent CYP2D6 inhibitory action

5) Some antiemetics

6) Dopamine receptor stimulants (dopamine agonists)

7) Dopamine precursors

8) MAO inhibitors

9) Central nervous system stimulants

10) VMAT2 inhibitors other than the study drug

11) Deep brain stimulation therapy

12) Supplements and foods containing ginkgo leaf extract

13) Vitamin E preparations and supplements

14) Yi-gan san (yokukan-san)

7. Criteria for Withdrawal of Subjects

7.1 Criteria for Discontinuation of Study Treatment

If any of the following criteria are met, the investigator (or subinvestigator) will discontinue the study treatment for the relevant subject.

(1) Upon request from the subject to discontinue participation in the study

(2) If the investigator (or subinvestigator) decides it not appropriate to continue the study treatment due to exacerbation of the underlying disease

(3) If the investigator (or subinvestigator) decides it difficult to continue the study treatment for the subject due to an adverse event, etc.

(4) If C-SSRS assessment indicates a suicide attempt or suicidal ideation corresponding to Item 4 or 5.

(5) If any of the following laboratory abnormalities (and adverse events) are observed.

1) Liver function test values

- ALT or AST >8×ULN
- ALT or AST >5×ULN for 2 weeks or longer
- ALT or AST >3×ULN, AND total bilirubin >2×ULN or PT-INR >1.5
- ALT or AST >3×ULN, AND occurrence of fatigue, nausea, vomiting, right upper abdominal pain/tenderness, fever, rash, or eosinophilia (> 5%)

2) Serum creatinine

- Subjects with a baseline serum creatinine level not exceeding the ULN
  - Serum creatinine >1.5×baseline level, AND serum creatinine >ULN for 2 weeks or longer
- Subjects with a baseline serum creatinine level exceeding the ULN

- Serum creatinine >1.5×baseline level for 2 weeks or longer

(6) If QTcF is 500 msec or more, or a clinically significant abnormality is observed on 12-lead ECG

(7) If it is found that the continuation of the study is not feasible due to the subject's circumstances, etc.

(8) If it is found that the subject is pregnant

(9) If the sponsor notifies that the study treatment should be discontinued

(10) Other cases where the investigator (or subinvestigator) decides that the study treatment for the subject should be discontinued

7.2 Criteria for Study Discontinuation

If any of the following criteria are met, the investigator (or subinvestigator) will discontinue the study for the relevant subject.

(1) Upon request from the subject to discontinue participation in the study

(2) If it is found that the continuation of the study is not feasible due to the subject's circumstances, etc.

(3) If the sponsor notifies that the study should be discontinued

(4) Other cases where the investigator (or subinvestigator) decides the study for the subject should be discontinued

8. Endpoints

8.1 Efficacy Endpoints

(1) Primary efficacy endpoint

- Change from baseline in the AIMS total score (Items 1 to 7; central assessment [redacted]) at Week 6
- Percentage of subjects with a 50% or greater improvement from baseline in the AIMS total score (Items 1 to 7; central assessment [redacted]) at Week 6
- Change from baseline in the AIMS total score (Items 1 to 12; assessment by the investigator [or subinvestigator]) at Week 6

- CGI-TD score at Week 6

(2) Exploratory endpoint

- Changes in the EQ-5D-5L score at each assessment point

8.2 Safety

- All subjects

(1) Adverse events and adverse drug reactions

(2) Clinical laboratory tests

(3) Vital signs

(4) Physical findings

(5) 12-lead ECGs

(6) C-SSRS

(7) SAS

(8) BARS

(9) MMSE-J

- Only subjects with schizophrenia or schizoaffective disorder

(10) JCDSS

(11) PANSS

- Only subjects with bipolar disorder or depressive disorder

(12) MADRS-J

(13) YMRS

8.3 Pharmacokinetic

Plasma drug concentrations of MT-5199, NBI-98782, and NBI-136110

9. Target Sample Size

240 patients (Double-blind period: 80 patients per group)

10. Study Period

April 2017 to December 2020

11. Schedule of Examinations/Observations

• Subjects with schizophrenia or schizoaffective disorder

Examinations/ observations etc.	Informed consent	Pre-treatment observation period		Double-blind period			Extension period											Post-treatment observation period
Visit		Screening (Day −29 to Day −1)	Baseline (Day −8 to Day −1)	W2	W4	W6 [Discontinuation*2]	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48 [Discontinuation*2]	Fu4w*1 [Discontinuation*2 +4w]
Allowable time window (day)				±3	±3	±3[+3]	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7[+3]	+7[+7]
Visit No.	-	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Informed consent	X																	
Subject demographics	X	X																
Inclusion/exclusion criteria	X	X	Update															
Complications		X	Update															
Physical measurements*3		X	(X)*7	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Infection and virus tests		X																
Pregnancy test*4		X	(X)*7	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CYP2D6 genotyping			X															
AIMS [redacted]		X	X	X	X	X			X				X				X	X
CGI-TD						X											X	X
EQ-5D-5L		X				X											X	X
Clinical laboratory tests*5		X	(X)*7	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum prolactin		X	(X)*7	X	X	X	X		X		X		X		X		X	X
Vital signs		X	(X)*7	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead electrocardiogram		X	(X)*7	X	X	X	X	X	X	X	X	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
JCDSS			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SAS			X	X	X	X	X		X		X		X		X		X	X
BARS			X	X	X	X	X		X		X		X		X		X	X
MMSE-J			X			X		X				X					X	
PANSS			X			X			X				X				X	
Drug concentration measurement				X	X	X			X				X				X	X
Study drug administration				<═══	═══	═══>	<═══	═══	═══	═══	═══	═══	═══	═══	═══	═══	═══>	
Study drug compliance				X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Examinations/ observations etc.	Informed consent	Pre-treatment observation period		Double-blind period			Extension period										Post-treatment observation period
Visit		Screening (Day −29 to Day −1)	Baseline (Day −8 to Day −1)	W2	W4	W6 [Discontinuation*2]	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48 [Discontinuation*2]	Fu4w*1 [Discontinuation*2 +4w]
Allowable time window (day)				±3	±3	±3[+3]	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7[+3]	+7[+7]
Visit No.	-	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Adverse events				<═══	═══	═══	═══	═══	═══	═══	═══	═══	═══	═══	═══	═══	═══	═══>
Concomitant medications*6	<═══	═══	═══	═══	═══	═══	═══	═══	═══	═══	═══	═══	═══	═══	═══	═══	═══	═══>

*1: 4th week of the post-treatment observation period *2: At the time of discontinuation of study treatment *3: Height and body weight will be measured at screening, and only body weight will be measured at other visits. *4: Only for women of childbearing potential.

*5: HbA1c will be measured only at screening, at baseline, at W6 or at the time of discontinuation in the double-blind period, at W12, W24, W36, and W48 or at the time of discontinuation in the extension period, and at Fu4w or 4 weeks after discontinuation of study treatment.

*6: Drugs used to treat TD, schizophrenia, schizoaffective disorder, bipolar disorder, or depressive disorder, and extrapyramidal symptoms will be investigated for the period from 90 days before the start of the pre-treatment observation period, and drugs used for other purposes will be investigated for the period after baseline.

*7: Screening data may be used as baseline data if the screening test is performed within the allowable time window for the baseline (Day −8 to Day −1).

• Subjects with bipolar disorder or depressive disorder

Examinations/ observations etc. / Visit	Informed consent	Pre-treatment observation period		Double-blind period			Extension period											Post-treatment observation period
		Screening (Day −29 to Day −1)	Baseline (Day −8 to Day −1)	W2	W4	W6 [Discontinuation*2]	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48 [Discontinuation*2]	Fu4w*1 [Discontinuation*2 +4w]
Allowable time window (day)		±3	±3	±3	±3	±3[+3]	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7[+3]	+7[+7]
Visit No.	-	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Informed consent	X																	
Subject demographics	X	X																
Inclusion/exclusion criteria	X	X	Update															
Complications		X	Update															
Physical measurements*3		X	(X)*7	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Infection and virus tests		X																
Pregnancy test*4		X	(X)*7	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CYP2D6 genotyping			X															
AIMS [redacted]		X	X	X	X	X			X				X				X	X
CGI-TD						X											X	X
EQ-5D-5L		X				X											X	X
Clinical laboratory tests*5		X	(X)*7	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum prolactin		X	(X)*7	X	X	X	X		X		X		X		X		X	X
Vital signs		X	(X)*7	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead electrocardiogram		X	(X)*7	X	X	X	X	X	X	X	X	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
MADRS-J			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SAS			X	X	X	X	X		X		X		X		X		X	X
BARS			X	X	X	X	X		X		X		X		X		X	X
MMSE-J			X			X		X				X					X	
YMRS			X			X			X				X				X	
Drug concentration measurement				X	X	X			X				X				X	X
Study drug administration				<═══	═══	═══>	<═══	═══	═══	═══	═══	═══	═══	═══	═══	═══	═══>	
Study drug compliance				X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Examinations/ observations etc.	Informed consent	Pre-treatment observation period		Double-blind period			Extension period										Post-treatment observation period
Visit		Screening (Day −29 to Day −1)	Baseline (Day −8 to Day −1)	W2	W4	W6 [Discontinuation*2]	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48 [Discontinuation*2]	Fu4w*1 [Discontinuation*2 +4w]
Allowable time window (day)				±3	±3	±3[+3]	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7[+3]	+7[+7]
Visit No.	-	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Adverse events				⟸	═	═	═	═	═	═	═	═	═	═	═	═	═	⟹
Concomitant medications*6	⟸	═	═	═	═	═	═	═	═	═	═	═	═	═	═	═	═	⟹

*1: 4th week of the post-treatment observation period *2: At the time of discontinuation of study treatment *3: Height and body weight will be measured at screening, and only body weight will be measured at other visits. *4: Only for women of childbearing potential.

*5: HbA1c will be measured only at screening, at baseline, at W6 or at the time of discontinuation in the double-blind period, at W12, W24, W36, and W48 or at the time of discontinuation in the extension period, and at Fu4w or 4 weeks after discontinuation of study treatment.

*6: Drugs used to treat TD, schizophrenia, schizoaffective disorder, bipolar disorder, or depressive disorder, and extrapyramidal symptoms will be investigated for the period from 90 days before the start of the pre-treatment observation period, and drugs used for other purposes will be investigated for the period after baseline.

*7: Screening data may be used as baseline data if the screening test is performed within the allowable time window for the baseline (Day −8 to Day −1).

1 RATIONALE AND BACKGROUND INFORMATION OF THE STUDY PLAN

1.1 Target Disease and Treatment Method

Tardive dyskinesia (TD) is a neurological condition characterized by involuntary movements of the orofacial region (ie, tongue, lips, jaw, face), extremities, and trunk. A common initial symptom is mild involuntary movement, but the severity of the disease and the degree of physical disability increase in many patients. While the majority of patients with mild disease are unaware of involuntary movement and do not often seek treatment, moderate and severe disease results in physical disability and may significantly interfere with daily life[1)].

TD is often caused by long-term administration of neuroleptics, such as dopamine receptor antagonists, and it is not uncommon that TD persists even when the causative agent is discontinued or replaced. Although the pathogenesis has not been fully elucidated, long-term administration of neuroleptics is thought to cause increased sensitivity of nigrostriatal dopamine receptors, resulting in the onset of TD[2)]. Long-term administration of neuroleptics is included in the diagnostic criteria for TD in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5).

Tetrabenazine, which inhibits the vesicular monoamine transporter 2 (VMAT2) like MT-5199, has been approved for the treatment of TD in European countries, Canada, and other countries. However, tetrabenazine has not been approved for this indication in Japan, and no therapeutic drugs for TD are available in this country.

1.2 Name and Description of the Investigational Product

MT-5199 is a valine-esterified oral prodrug of (+)α-dihydrotetrabenzazine (NBI-98782), the most selective optical isomer for VMAT2 among the four metabolites of tetrabenazine, and it was discovered by Neurocrine Biosciences in the United States.

MT-5199, after being reduced to the active metabolite NBI-98782, selectively inhibits VMAT2 in vesicles at the presynaptic site, thereby inhibiting monoamine uptake and decreasing the amount of dopamine released into the synaptic cleft. MT-5199 is thus expected to have the effect of normalizing the function of the dopamine nervous system involved in the development of involuntary movement. Since MT-5199 is reduced to NBI-98782 only, there is no concern about the off-target effects (inhibition of dopamine D_2 and serotonin 5-HT receptors) of other optical isomers of tetrabenazine metabolites.

Neurocrine Biosciences has obtained approval from the U.S. Food and Drug Administration (FDA) for MT-5199 as a treatment drug for TD. [redacted] Mitsubishi Tanabe Pharma Corporation has acquired the right to develop MT-5199 in Japan and other Asian countries from Neurocrine Biosciences, and is developing the drug for the indication of TD.

1.3 Nonclinical and Clinical Study Data

1.3.1 Nonclinical Study Data

MT-5199 causes little cytochrome P450 (CYP) enzyme inhibition or induction at pharmacologically relevant concentrations. It inhibits P-glycoprotein in the gastrointestinal tract, but is not an inhibitor of a panel of other drug transporters. The metabolism of MT-5199 is characterized by the formation of NBI-98782 by hydrolysis of MT-5199 and the formation of NBI-136110 by CYP3A4/5-mediated mono-oxidation. The metabolism of NBI-98782 primarily involves CYP2D6. MT-5199, NBI-98782, and NBI-136110 all have VMAT2 inhibitory effects, among which NBI-98782 is the most potent, being responsible for most of the pharmacological action due to VMAT2 inhibition. Repeat-dose toxicity studies in mice, rats, and dogs showed tolerability at doses of 60, 3, and 15 mg/kg/day, respectively. Systemic exposures to MT-5199 and NBI-98782 at the no-observed-adverse-effect levels (NOAEL) obtained in safety pharmacology studies in the central nervous system, respiratory system, and cardiovascular system were higher than systemic exposures at the highest clinical dose in humans. MT-5199 had a slight adverse effect at a dose of 10 mg/kg/day in a rat fertility study (NOAEL: 3 mg/kg/day). In embryo-fetal development studies in rats and rabbits, NOAELs were 15 and 50 mg/kg/day, respectively. No teratogenicity was observed in rats or rabbits. MT-5199 was negative in *in vitro* mutagenicity tests (Ames and chromosomal aberration tests), an *in vivo* micronucleus test in rats, and an *in vitro* phototoxicity test with BALB/c 3T3 cells.

1.3.2 Clinical Study Data

As of August 2019, the following 22 clinical studies have been completed in healthy adults, patients with hepatic impairment, or TD patients: 15 Phase I studies in healthy adults or patients with hepatic impairment (including a Japanese Phase I study), four overseas Phase II studies in patients with schizophrenia, schizoaffective disorder, mood disorder, or gastrointestinal disorder and TD, and three overseas Phase III studies in patients with schizophrenia, schizoaffective disorder, or mood disorder and TD.

In a Phase I study in healthy Japanese and non-Japanese adults, MT-5199 was rapidly absorbed after oral administration under fasted conditions, and C_{max} was reached in about 1 hour. The C_{max} of the active metabolite NBI-98782 was reached after 4 to 8 hours. The plasma concentrations of both MT-5199 and NBI-98782 decreased after C_{max} was reached, with the $t_{1/2}$ of about 20 hours. Thus, NBI-98782 is produced and eliminated slowly, resulting in a small variation from peak to trough concentrations. Multiple-dose administration of MT-5199 resulted in minimal accumulation of MT-5199, but NBI-98782 showed approximately 2-fold accumulation, with a steady state reached within 4 to 5 days. The C_{max} and AUC of MT-5199 and NBI-98782 increased in a dose-dependent manner at doses ranging from 40 mg to 80 mg.

When MT-5199 and ketoconazole were concomitantly administered to healthy adults, the C_{max} of MT-5199 and NBI-98782 increased 1.5-fold and 1.6-fold, respectively, and the AUC of NBI-98782 showed a 2.1-fold increase. Compared with MT-5199 alone, concomitant administration of MT-5199 and rifampin reduced the C_{max} and AUC of MT-5199 by about 30% and about 70%, respectively, and the C_{max} and AUC of NBI-98782 by about 50% and

about 80%, respectively. When MT-5199 80 mg and digoxin 0.5 mg were concomitantly administered, the C_{max} of digoxin increased approximately 1.9-fold. However, the AUC increased only slightly (1.4-fold), and the mean $t_{1/2}$ of digoxin was similar with and without coadministration of MT-5199. The C_{max} and AUC of midazolam were similar with and without coadministration of MT-5199. In patients with moderate or severe hepatic impairment, the C_{max} and AUC of MT-5199 and NBI-98782 were about 2 to 3 times higher than in individuals with normal hepatic function.

With regard to the efficacy of MT-5199 in TD patients, an overseas Phase II double-blind placebo-controlled study (Study NBI-98854-1202 [hereinafter, "Study 1202"]), in which the dose was increased gradually for 6 weeks (25 mg/day, 50 mg/day, and 75 mg/day administered at intervals of 2 weeks), showed a statistically significant decrease in the change in the total score of Abnormal Involuntary Movement Scale (AIMS) Items 1 to 7 in the MT-5199 group as compared with the placebo group. In an overseas Phase III study (Study NBI-98854-1304 [hereinafter, "Study 1304"]), MT-5199 at doses of 40 mg/day and 80 mg/day for 6 weeks resulted in a statistically significant improvement in the change in the total score of AIMS Items 1 to 7 in both dose groups as compared with the placebo group. In both studies, the response rate (percentage of patients with a 50% or greater improvement in the total score of AIMS Items 1 to 7) was statistically significantly higher in the MT-5199 group than in the placebo group.

Final data on the safety of MT-5199 in TD patients are available from overseas Phase II studies (Studies NBI-98854-1201 and 1202) and overseas Phase III studies (Studies 1304 and NBI-98854-1402). In a 6-week placebo-controlled study of MT-5199, the adverse events of which the incidence was 5% or higher in the MT-5199 group and was also higher in the MT-5199 group than in the placebo group were somnolence (including fatigue and sedation; 10.9% in the MT-5199 group and 4.2% in the placebo group) and anticholinergic effects (dry mouth, constipation, disturbance in attention, vision blurred, urinary retention; 5.4% in the MT-5199 group and 4.9% in the placebo group). The adverse events with an incidence of 5% or higher with long-term administration (up to 48 weeks) were headache (7.7%), urinary tract infection (7.4%), somnolence (6.3%), and fatigue (5.1%). No safety signals related to the cardiovascular system, laboratory test values, or vital signs were detected.

To date, a total of eight deaths have been reported in overseas clinical studies of MT-5199 (including clinical studies enrolling TS patients), consisting of seven deaths in the MT-5199 group (one subject each died of sudden death; hyperkalemia, heart failure, hepatic failure, diabetes, metabolic acidosis, and pleural effusion; breast cancer; chronic obstructive pulmonary disease; sepsis syndrome; coma; and hypertensive heart disease) and one death in the placebo group (the subject died of myocardial infarction). All of the adverse events were considered not related or unlikely related to the study drug. Serious adverse events (SAE) were observed in 109 subjects. Of them, the SAEs that were considered possibly related to the study drug were acute hepatitis, suicidal ideation, confusional state, hypersensitivity, extrapyramidal disorder, and cognitive disorder (1 subject each), all of which were observed in the MT-5199 group. The SAEs reported in at least 3 subjects were schizophrenia (7 subjects), suicidal ideation (6 subjects), chronic obstructive pulmonary disease (5 subjects), mental status changes, syncope, and schizoaffective disorder (4 subjects each), and depression, abdominal pain, and psychotic disorder (3 subjects each).

1.4 Plan for This Study

Based on the fact that the pharmacokinetics of MT-5199 were similar between Japanese and non-Japanese subjects in a Japanese Phase I study (Study MT-5199-J01 [hereinafter, "Study J01"]), it was planned to conduct a Japanese Phase II/III study and its long-term extension study in TD patients.

In this study, the efficacy and safety data of MT-5199 (40 mg and 80 mg) in TD patients will be collected [redacted].

2 STUDY OBJECTIVES

The objective of this study is to evaluate the efficacy and safety of MT-5199 (40 mg or 80 mg) administered once daily in patients with clinical diagnoses of schizophrenia or schizoaffective disorder, or bipolar disorder or depressive disorder and TD.

- The superiority of MT-5199 (40 mg and 80 mg) over placebo will be tested by using the change from baseline in the AIMS total score (Items 1 to 7; central assessment [redacted]) at Week 6 as an index.
- The safety of 6-week treatment with MT-5199 (40 mg/day or 80 mg/day), as well as the efficacy and safety during a 42-week extension period, will be evaluated.

3 STUDY SUBJECTS

3.1 Study Subjects

Patients with clinical diagnoses of schizophrenia or schizoaffective disorder, or bipolar disorder or depressive disorder and TD

3.2 Inclusion Criteria

Patients who satisfy all of the following inclusion criteria, have an adequate understanding of the study, and have given written consent to participate in the study will be enrolled.

(1) Men and women aged 20 to 85 years at the time of informed consent obtainment

(2) Patients diagnosed with schizophrenia, schizoaffective disorder, bipolar disorder, or depressive disorder according to the diagnostic criteria of DSM-5 at least 3 months before informed consent obtainment

(3) Patients diagnosed with TD (DSM-5 code: 333.85) according to the diagnostic criteria of DSM-5 prior to informed consent obtainment

(4) Patients judged to be with moderate or severe TD (AIMS Item 8, severity of abnormal movement overall) on central AIMS assessment [redacted]

(5) Patients in whom the dosage regimen of maintenance therapy drugs for schizophrenia, schizoaffective disorder, bipolar disorder, or depressive disorder, and psychotropic drugs used for extrapyramidal symptoms, etc. have not been changed since at least 30 days before the start of the pre-treatment observation period (or, for benzodiazepines, at least 14 days before the start of the pre-treatment observation period)

(6) (If maintenance therapy drugs are not used for schizophrenia, schizoaffective disorder, bipolar disorder, or depressive disorder) Patients whose psychiatric symptoms are stable as judged by the investigator (or subinvestigator) during the pre-treatment observation period

(7) Patients with a BMI $\geq$ 17.0 and $<$ 35.0 at screening (BMI calculation formula: body weight (kg)/height $(m)^2$, rounded to second decimal place)

[redacted]

[redacted]

3.3 Exclusion Criteria

Patients who fall under any of the following exclusion criteria will be excluded from the study.

- All subjects

(1) Patients with active, clinically significant, unstable cerebrovascular disease, hepatic disease, renal disease, endocrine disease, cardiovascular disease, gastrointestinal disease, respiratory disease, metabolic disease, etc. during the pre-treatment observation period (refer to Grade 3 in [redacted] "Criteria for Classification of the Seriousness of Adverse Reactions to Pharmaceuticals, etc.")

(2) Patients diagnosed with dementia according to the diagnostic criteria of DSM-5 during the pre-treatment observation period

(3) Patients judged to be with prominent abnormal involuntary movements, such as coexisting dystonia, akathisia, or parkinsonism, and TD which cannot be properly evaluated on central AIMS assessment [redacted]

(4) Patients with an SAS score of 3 or greater at baseline in two or more items (except Items 8 and 10)

(5) Patients with substance-related disorder (except tobacco- or caffeine-related disorder) according to the diagnostic criteria of DSM-5 within 3 months before initial randomization

(6) Patients at high risk of suicidal or self-injurious behavior as judged by the investigator (or subinvestigator), and patients with suicidal attempts or suicidal ideation corresponding to Item 4 or 5 on C-SSRS assessment at baseline (within 3 months before evaluation)

(7) Patients with a history of neuroleptic malignant syndrome within 3 years before initial randomization

(8) Patients with a history of long QT syndrome or tachyarrhythmia within 3 years before initial randomization

(9) Patients with a QTcF ≥450 msec (men) or ≥470 msec (women) on a standard 12-lead electrocardiogram (ECG) at screening

(10) Patients with laboratory abnormalities at screening (However, those who fall under "3) only (γ-GTP ≥3×ULN)" may be enrolled, subject to the approval of the sponsor's medical expert).

1) Serum creatinine >1.5×ULN

2) ALT or AST ≥2.5×ULN

3) γ-GTP ≥3×ULN

4) Total bilirubin >1.5 mg/dL

5) Hemoglobin <10 g/dL

6) White blood cell count <3,000/mm^3

7) Platelet count <100,000/mm^3

(11) Patients with a history of malignant tumor within 3 years before initial randomization. However, complete excision of basal cell carcinoma or squamous cell carcinoma of the skin is excluded.

(12) Patients who tested positive for HBs antigen, HCV antibody, or HIV antibody in the Infection and virus tests at screening (However, HCV antibody-positive patients may be enrolled only if HCV RNA testing is negative).

(13) Patients who have received another investigational drug within 6 months before initial randomization

(14) Patients with previous treatment with deep brain stimulation within 3 years before initial randomization

(15) Patients with a history of surgery known to affect digestive tract absorption of drugs

(16) Patients with a history of drug allergy or previous tetrabenazine administration (However, patients with a history of drug allergy may be enrolled, subject to the approval of the sponsor's medical expert).

(17) Patients who do not agree to use appropriate contraception from the time of informed consent obtainment until 28 days after the completion (discontinuation) of study treatment

(18) Female patients who are pregnant, breastfeeding, or possibly pregnant

(19) Other patients who are ineligible for this study as judged by the investigator (or subinvestigator).

- Subjects with schizophrenia or schizoaffective disorder

(20) Patients with a total JCDSS (Calgary Depression Scale for Schizophrenics, Japanese Version) score of 10 or higher at baseline

(21) Patients with a total PANSS score of 70 or higher at baseline

- Subjects with bipolar disorder or depressive disorder

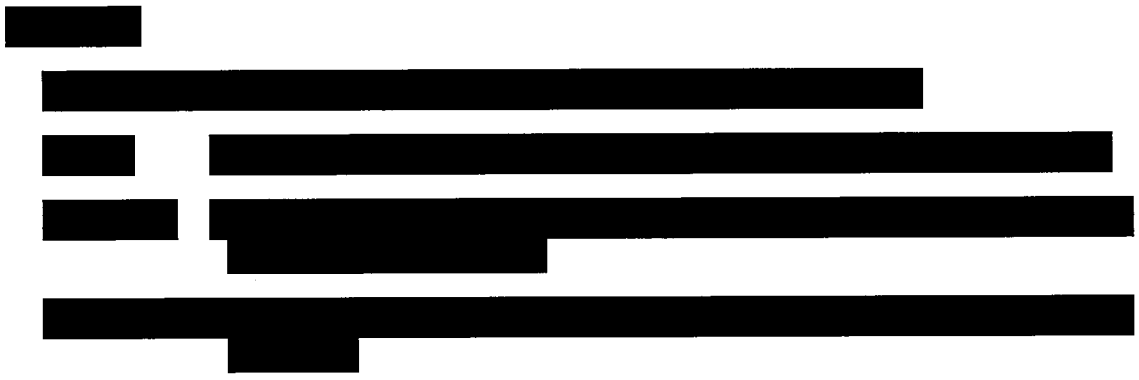
(22) Patients hospitalized for treatment of bipolar disorder or major depressive disorder within 6 months before initial randomization

(23) Patients with mood episodes (manic symptoms and depressive symptoms) within 3 months before initial randomization

(24) Patients with a history of rapid cycling (more than four episodes in a year) or ultra-rapid cycling (more than four episodes in a month)

(25) Patients with a total MADRS-J score of more than 13 at baseline

(26) Patients with a total YMRS score of more than 10 at baseline



4 SUBJECT INFORMATION AND CONSENT

4.1 Preparation of the Written Information for Patients and the Informed Consent Form

The investigator will prepare the written information for patients and the informed consent form (hereinafter referred to as informed consent documents). The informed consent documents will be handled as a set of documents and amended as needed.

The informed consent documents and their amendments will be submitted to the sponsor, and to the institutional review board (IRB) to obtain approval before the start of the study.

4.2 Contents That Should Be Included in the Written Information for Patients

The written information for patients should include at least the following issues:

(1) Involving research in the study,

(2) The purpose of the study,

(3) Name, title, and contact information of the investigator (or subinvestigator),

(4) Study methods (including the research aspect of the study, subject inclusion criteria, and the probability of random assignment to each treatment if any),

(5) The expected clinical benefits and risks or inconveniences (when there is no expected benefit to the subject, the subject should be notified of this matter),

(6) Alternative treatment(s) that may be available to the subject and their important potential benefits and risks if the study is conducted in patients,

(7) Expected duration of the subject's participating in the study,

(8) That participation in the study should be voluntary and that the subject is free to refuse participation in the study and to withdraw from the study at any time without penalty or loss of benefits to which the subject is otherwise entitled,

(9) That the monitors, auditors, IRB members, and regulatory authorities can have direct access to source medical documents, that the confidentiality of subjects is protected at the time of such access, and that the subject's signature or personal seal affixed to the informed consent form means acknowledgement of such access,

(10) That the confidentiality of subjects is protected if results of the study are published,

(11) Study site personnel to contact for further information regarding the study and rights of subjects or in the event of a study-related health injury,

(12) Compensation and treatment for health injury that the subject is entitled to receive in the event of a study-related health injury,

(13) Issues related to the IRB of this study, including the type of IRB reviewing and discussing the validity of the study, and items to be reviewed and discussed in each IRB meeting,

(14) Planned number of subjects to be involved in the study,

(15) That information that may be relevant to the subject's willingness to continue participating in the study will be available to the subject in a timely manner,

(16) Conditions and/or reasons for the subject's withdrawal from the study,

(17) Anticipated expenses, if any, to be covered by the subject,

(18) Anticipated payment, if any, to be provided to the subject (e.g., prearranged rules for calculation of the amount to be paid), or

(19) The subject's responsibilities.

4.3 Method of Informed Consent Obtainment

(1) Before the conduct of the study, the investigator (or subinvestigator) will provide prospective patients with the IRB-approved informed consent documents, and fully explain the details of the study. Clinical study collaborators may provide supplemental explanations to patients. The investigator (or subinvestigator) must use language readily understandable to patients when providing explanations about the study based on the written information for patients and fully answer any questions from patients. After confirming that patients fully understand the contents of the study, the investigator (or subinvestigator) will obtain voluntary written informed consent to participate in the study from each patient.

(2) The investigator (or subinvestigator) who has provided the explanations and the patient will sign or seal and date the informed consent form. The clinical study collaborators who have given supplementary explanations will also sign or seal and date the form.

(3) Prior to the subject's entry into the study, the investigator (or subinvestigator) will provide the subject with a copy of the signed or sealed and dated informed consent documents, and retain the original informed consent form appropriately according to the regulations of the relevant study site.

(4) The date of informed consent will be recorded in the case report form.

4.4 Amendments to the Informed Consent Documents

(1) If new important information that can possibly affect the subject's consent is obtained, the investigator (or subinvestigator) will verbally share such information in a prompt manner with subjects already participating in the study, confirm their willingness to continue participation in the study, and document the matter in the medical record.

(2) The investigator will decide whether to amend the informed consent documents based on such information in a timely manner.

(3) If an amendment is considered necessary, the investigator must promptly amend the informed consent documents and reobtain approval of the IRB.

(4) The investigator (or subinvestigator) will provide explanations to subjects already participating in the study by using the IRB-reapproved informed consent documents and reobtain voluntary written informed consent to continue participation in the study from each subject.

(5) In the same manner as the first informed consent, the investigator (or subinvestigator) who has provided the explanation and the subject will sign or seal and date the informed consent form. The clinical study collaborators who have given supplementary explanations will also sign or seal and date the form.

(6) The investigator (or subinvestigator) will provide subjects with a copy of the signed or sealed and dated informed consent documents, and retain the original informed consent form appropriately according to regulations of the relevant study site.

5 STUDY DESIGN

5.1 Phase of Development and Type of Study

Phase of development: Phase II/III

Type of study: Confirmatory study

5.2 Study Design

This study is a Phase II/III, randomized, double-blind, placebo-controlled, multicenter, parallel-group, fixed-dose study. The study period consists of a pre-treatment observation period of up to 4 weeks, a double-blind period of 6 weeks (placebo-controlled study treatment period), a 42-week extension period (MT-5199 administration period), and a 4-week post-treatment observation period.

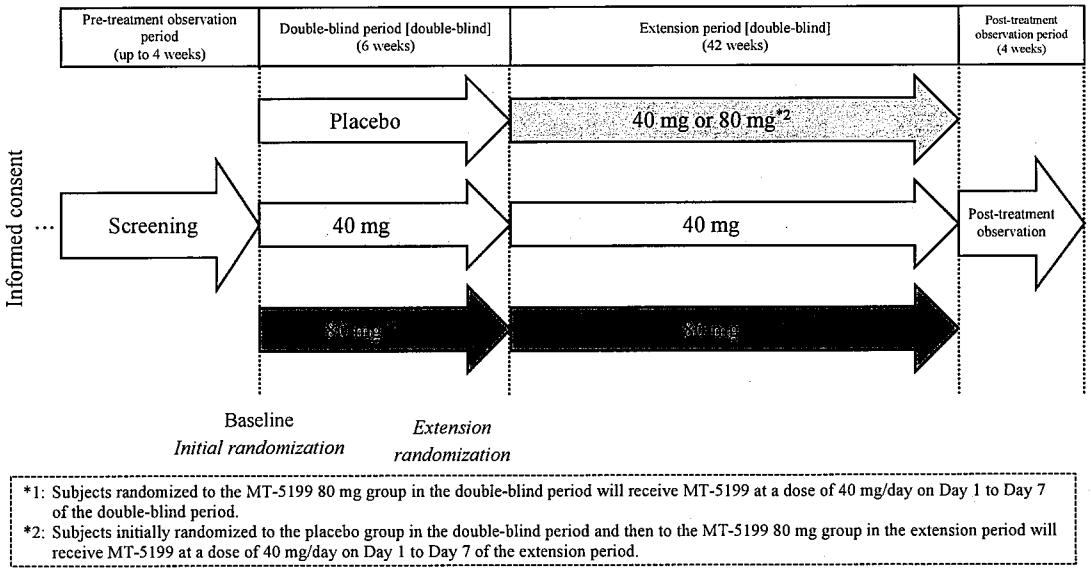


Figure 1 Overview of the Study Design

Subjects deemed eligible based on the inclusion and exclusion criteria will be randomized to the placebo group, MT-5199 40 mg group, or MT-5199 80 mg group at a ratio of 1:1:1 on the day of randomization (Initial randomization) and treated with the study drug for 6 weeks.

In the randomization prior to the start of the extension period (Extension randomization), subjects who were randomized to the placebo group in the initial randomization will be randomized to either the MT-5199 40 mg group or the MT-5199 80 mg group (at a

randomization ratio of 1:1), and subjects who were randomized to either of the MT-5199 groups in the initial randomization will be randomized to the same dose group.

Subjects randomized to the MT-5199 80 mg group in the double-blind period will receive MT-5199 at a dose of 40 mg/day on Day 1 to Day 7 of the double-blind period. Subjects randomized to the placebo group in the double-blind period and then to the MT-5199 80 mg group in the extension period will receive MT-5199 at a dose of 40 mg/day on Day 1 to Day 7 of the extension period.

(1) Pre-treatment observation period (up to 4 weeks)

The pre-treatment observation period is up to 4 weeks between the day of screening test/observation (except investigations related to Section 9.2.1 "Subject Demographics") and the day of initial randomization.

(2) Double-blind period (6 weeks)

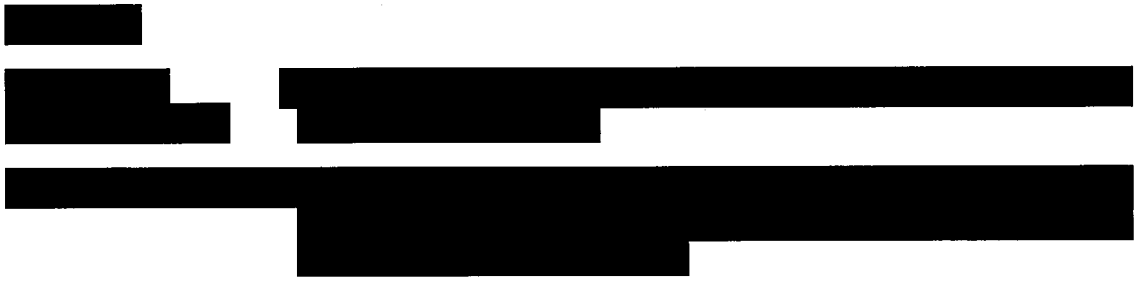
The double-blind period is 6 weeks from the following day of initial randomization. Scheduled visits should occur at Week 2, Week 4, and Week 6, counting from the start day of the double-blind period as Day 1. During this period, placebo, MT-5199 40 mg, or MT-5199 80 mg will be administered once daily in a double-blind manner.

(3) Extension period (42 weeks)

The extension period is 42 weeks from the following day of the end of the double-blind period. Scheduled visits should occur at Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, and Week 48, counting from the start day of the double-blind period as Day 1. During this period, MT-5199 40 mg or 80 mg will be administered once daily in a double-blind manner.

(4) Post-treatment observation period (4 weeks)

The post-treatment observation period is 4 weeks from the following day of the completion (discontinuation) of study treatment. A scheduled visit should occur at 4 weeks after the completion (discontinuation) of treatment.



[redacted]

5.3 Blinding and Randomization Methods

5.3.1 Blinding Method

(1) Management of the material list and the randomization key code table

[redacted]

(2) Confirmation of the indistinguishability of study drugs

[redacted]

(3) Management of drug concentration measurement results

The drug concentration measurement facility will not report the results of plasma drug concentration measurement to the sponsor or study sites until the key code is unblinded.

The drug concentration measurement facility will also strictly retain the copy of the material list until the key code is unblinded.

(4) Management of serum prolactin measurement results

The contract clinical laboratory will not report the results of serum prolactin

measurement after the start of study treatment to the sponsor or study sites until the key code is unblinded. Serum prolactin measurement outside the contract clinical laboratory is prohibited during the period from the start of study treatment until the end of the study period.

(5) Management of the emergency key and the SUSAR key

[redacted]

(6) Method of study drug administration

Subjects will take two capsules per day throughout the treatment period unless dose modification of the study drug is prescribed by the investigator (or subinvestigator) (see Section 8.3 "Dosage and Administration Method").

5.3.2 Randomization and Allocation Methods

(1) Initial randomization (before the start of the double-blind period)

At the time of transition from the pre-treatment observation period to the double-blind period, subjects deemed eligible based on the inclusion and exclusion criteria will be randomized [redacted] to the placebo group, MT-5199 40 mg group, or MT-5199 80 mg group at a ratio of 1:1:1. [redacted]

[redacted]

(2) Extension randomization (before the start of the extension period)

At the time of transition from the double-blind period to the extension period, subjects who were randomized to the placebo group in the initial randomization will be randomized [redacted] to either the MT-5199 40 mg group or the MT-5199 80 mg group at a ratio of 1:1. [redacted] Subjects who were randomized to the MT-5199 40 mg group or the MT-5199 80 mg group in the initial randomization will be assigned to the same dose group as in the double-blind period.

5.4 Endpoints

5.4.1 Efficacy Endpoints

(1) Primary efficacy endpoint

- Change from baseline in the AIMS total score (Items 1 to 7; central assessment [redacted]) at Week 6
- Percentage of subjects with a 50% or greater improvement from baseline in the AIMS total score (Items 1 to 7; central assessment [redacted]) at Week 6
- Change from baseline in the AIMS total score (Items 1 to 12; assessment by the investigator [or subinvestigator]) at Week 6
- CGI-TD score at Week 6

(2) Exploratory endpoint

- Changes in the EQ-5D-5L score at each assessment point

[redacted]

5.4.2 Safety Endpoints

- All subjects
  - (1) Adverse events and adverse drug reactions
  - (2) Clinical laboratory tests
  - (3) Vital signs
  - (4) Physical findings
  - (5) 12-lead ECGs
  - (6) C-SSRS
  - (7) SAS
  - (8) BARS
  - (9) MMSE-J
- Only subjects with schizophrenia or schizoaffective disorder
  - (10) JCDSS
  - (11) PANSS
- Only subjects with bipolar disorder or depressive disorder

(12) MADRS-J

(13) YMRS

[redacted]

5.4.3 Pharmacokinetic Endpoint

Plasma drug concentrations of MT-5199, NBI-98782, and NBI-136110

[redacted]

6 TARGET SAMPLE SIZE AND STUDY PERIOD

6.1 Target Sample Size

240 patients (Double-blind period: 80 patients per group)

[redacted]

6.2 Study Period

April 2017 to December 2020

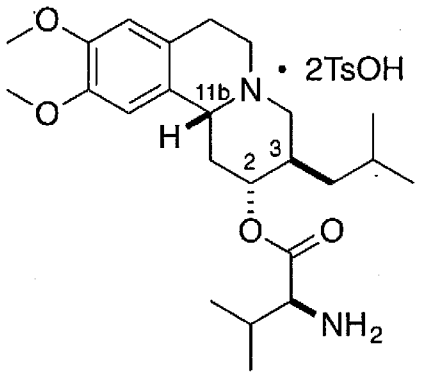
7 STUDY DRUGS

7.1 Names of Study Drugs

(1) Investigational product

MT-5199 40 mg capsule

- A capsule containing 40 mg free base equivalent of MT-5199 ditosylate salt
- International nonproprietary name: Valbenazine tosylate
- Molecular formula: $C_{38}H_{54}N_2O_{10}S_2$
- Molecular weight: 762.97
- Structural formula:



(2) Control drug

MT-5199 placebo capsule

- A capsule that is indistinguishable in appearance from the investigational product but does not contain MT-5199 ditosylate salt

7.2 Packaging and Labeling of Study Drugs

(1) Packaging

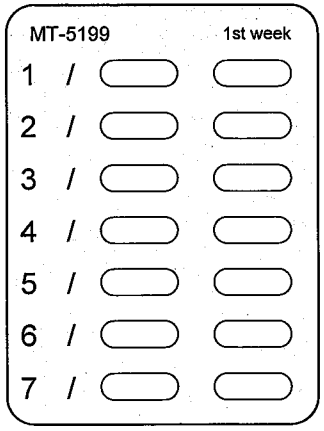
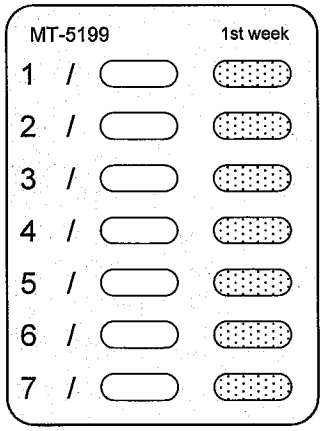
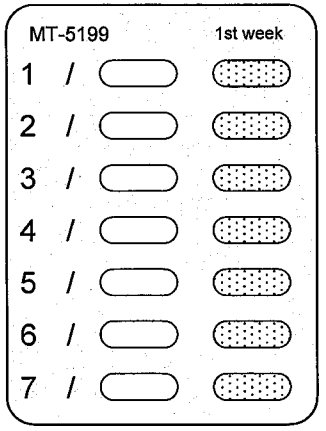
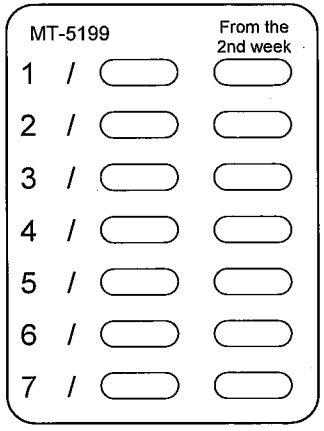
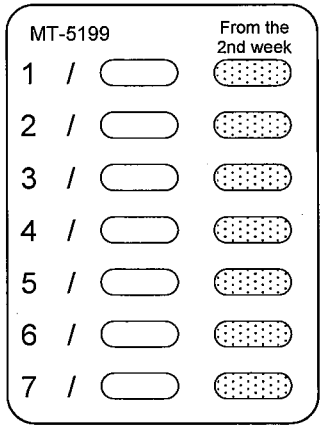
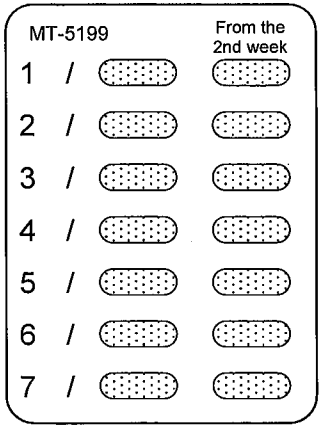
A 7-day (1-week) supply of study drugs for both the double-blind period and the extension period will be packaged in wallets. Two capsules (1 row) in a wallet will be taken daily, for a total of 14 capsules (7 rows) for 7 days.

For both the double-blind period and the extension period, the sheet of the wallet for the first week is light blue and the sheets for the second and subsequent weeks are

white in color, with the letters "For Week 1" and "From Week 2 onwards," respectively, printed on the upper right. In addition, the right column of the sheets for the extension period is surrounded by a red frame to indicate capsules to be taken in the event a change in dosage occurs.

1) Double-blind period

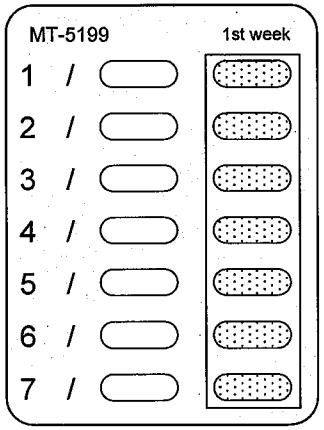
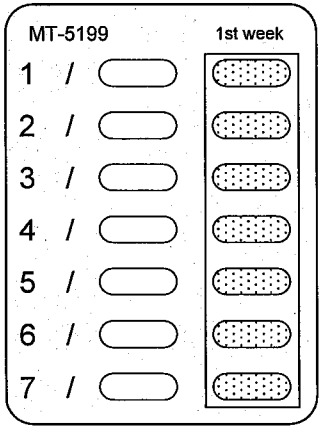
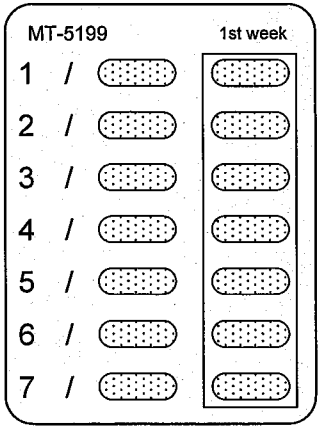
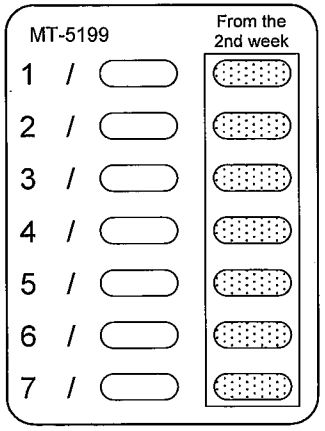
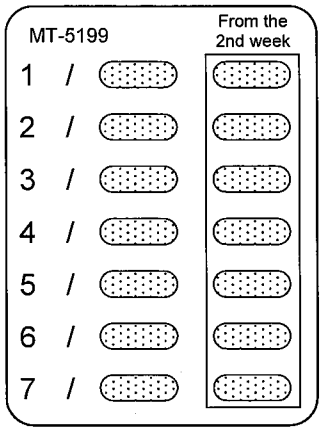
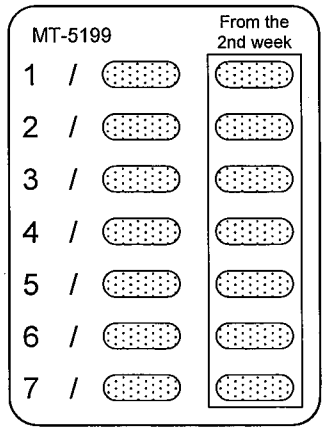
For the double-blind period, seven wallets (for the 1st to 6th weeks of the double-blind period plus an extra 1-week supply) will be put in an individual packaging box and the box will then be sealed.

Double-blind period	**Placebo group**	**40 mg group**	**80 mg group**
1st week (1 wallet)			
2nd to 6th weeks (6 wallets; including an extra 1-week supply)			

: MT-5199 placebo capsule : MT-5199 40 mg capsule

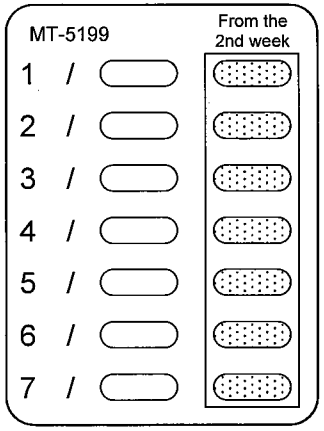
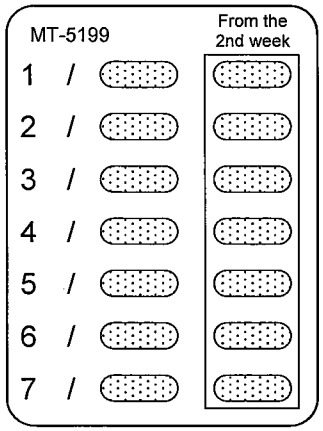
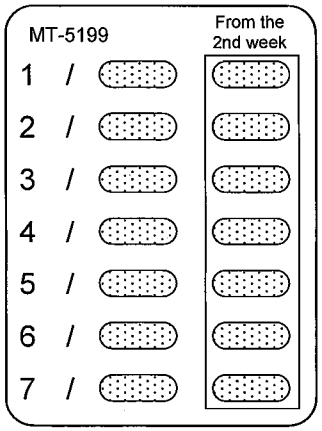
2) Extension period

For the first prescription in the extension period, seven wallets (for the 1st to 6th weeks of the extension period plus an extra 1-week supply) will be put in an individual packaging box and the box will then be sealed.

Extension period (First prescription)	**40 mg group**	**80 mg group (Transition from the placebo group)**	**80 mg group (Transition from the 80 mg/day group)**
• 1st week (1 wallet)			
• 2nd to 6th weeks (6 wallets; including an extra 1-week supply)			

: MT-5199 placebo capsule : MT-5199 40 mg capsule

For the second, third, and fourth prescriptions in the extension period, 13 wallets each (for the 7th to 18th weeks of the extension period plus an extra 1-week supply; for the 19th to 30th weeks of the extension period plus an extra 1-week supply; and for the 31st to 42nd weeks of the extension period plus an extra 1-week supply) will be put in an individual packaging box and the box will then be sealed.

Extension period (Second, third, and fourth prescriptions)	**40 mg group**	**80 mg group (Transition from the placebo group)**	**80 mg group (Transition from the 80 mg/day group)**
• 7th to 18th weeks • 19th to 30th weeks • 31st to 42nd weeks (13 wallets each; including an extra 1-week supply)			

: MT-5199 placebo capsule : MT-5199 40 mg capsule

(2) Labeling

1) Double-blind period

Top of the individual packaging box

For clinical study use　　Drug No.: XXXXX

Study MT-5199-J02 <Double-blind period>

For one patient (6-week supply [84 capsules] plus extra 1-week supply [14 capsules])

Storage: At room temperature　　Lot No.: XXXXX

[redacted]

Mitsubishi Tanabe Pharma Corporation

* For handling, storage, and management of this study drug, please refer to the procedural document provided separately.
* After completion of the clinical study, unused drugs and empty boxes will be collected.

Front and right side of the individual packaging box

Study MT-5199-J02
<Double-blind period>

Mitsubishi Tanabe Pharma Corporation

Wallet

For clinical study use　　Drug No.: XXXXX

Study MT-5199-J02 <Double-blind period>

One-week supply (14 capsules)
Take two capsules every morning.*

This sheet should not be discarded but should be returned.

At room temperature

[redacted]

Mitsubishi Tanabe Pharma Corporation

* If a change is made to the time of administration, the printed information should be corrected.

2) Extension period

Top of the individual packaging box

For clinical study use　　Drug No.: XXXXX

Study MT-5199-J02 <Extension period>

For one patient (xx-week supply [xxx capsules] plus extra 1-week supply [14 capsules])

Storage: At room temperature　　Lot No.: XXXXX

[redacted]
Mitsubishi Tanabe Pharma Corporation

* For handling, storage, and management of this study drug, please refer to the procedural document provided separately.
* After completion of the clinical study, unused drugs and empty boxes will be collected.

* For the first prescription　　: 6-week supply [84 capsules]
For the second, third, and fourth prescriptions　　: 12-week supply [168 capsules]

Front and right side of the individual packaging box

Study MT-5199-J02
<Extension period>

Mitsubishi Tanabe Pharma Corporation

Wallet

For clinical study use　　Drug No.: XXXXX

Study MT-5199-J02 <Extension period>

One-week supply (14 capsules)
Take two capsules every morning. *

Take only one capsule in the right column (within the red frame) every morning if your doctor instructs you to reduce the dose. **

This sheet should not be discarded but should be returned.

At room temperature

[redacted]
Mitsubishi Tanabe Pharma Corporation

* If a change is made to the time of administration, the printed information should be corrected.
** Indicated for Week 2 onwards only.

7.3 Storage Conditions

At room temperature (1°C to 30°C)

7.4 Methods of Handling, Storage, and Management of Study Drugs

The sponsor will supply study drugs after conclusion of a study contract between the sponsor and the study site.

The study drug manager will store and manage the study drugs according to "Procedure for Study Drug Management" stipulated by the sponsor, and return unused study drugs to the sponsor after the end of the study.

The study drugs must not be used for any other purpose than as specified in the protocol (other clinical studies, animal experiments, basic experiments, etc.).

7.5 Procedures for Emergency Key Unblinding

(1) If there is an urgent need to identify the study drug to ensure the safety of study subjects, such as when a serious adverse event occurs, the investigator will respond in accordance with the "Procedure for Emergency Key Unblinding." In that case, the investigator should promptly document the reason for unblinding the emergency key and submit it to the sponsor.

(2) If a safety concern arises that can affect the risk/benefit profile of the study drug and there is an urgent need to identify the study drug, the sponsor's person engaged in clinical study safety management will respond in accordance with the" Procedure for Emergency Key Unblinding." The sponsor's person engaged in clinical study safety management will document the reason for unblinding the emergency key and the content of deliberations and retain the record in accordance with the in-house procedures.

8 STUDY PROCEDURES FOR SUBJECTS

8.1 Preparation of Subject Screening, Registration, and Subject Identification Code Lists

The investigator will prepare a subject screening log that lists subjects who have provided written informed consent. The investigator will also prepare a subject identification code list in which each subject is assigned an identification code. In this process, information necessary for reconciliation with source documents should be described in the list.

In addition, the investigator will prepare a subject registration log that lists the sex, date of informed consent, subject identification code, etc. of subjects who have provided written informed consent.

Upon request by the sponsor, the investigator will provide the subject screening list, while fully ensuring protection of subjects' privacy and personal information.

8.2 Subject Registration

Clinical study collaborators may input data into the Web-based subject registration system, as described below, if necessary information is recorded in source documents such as medical records.

(1) Informed consent obtainment

The investigator (or subinvestigator) will select patients who are deemed eligible for this study and obtain their written informed consent for voluntary participation in accordance with Section 4 "Subject Information and Consent." [redacted]

(2) The start of the pre-treatment observation period

[redacted]

(3) Initial randomization

On Day −1 (day before the scheduled day of the start of the double-blind period [start of study treatment]), the investigator (or subinvestigator) will confirm that the subject meets the inclusion criteria and does not fall under any of the exclusion criteria (including the result of central AIMS assessment), [redacted] and confirm the judgment of the initial randomization. If the judgment is "appropriate," the drug number issued will be confirmed and the appropriate study drug will be prescribed. The drug number of the study drug will be assigned from among the drug numbers of the study drugs

delivered in advance from the sponsor before the drug number is issued.

(4) Discontinuation before initial randomization

[redacted]

(5) Extension randomization and issuance of the drug number of the study drug for the extension period (first prescription in the extension period)

[redacted]

The investigator (or subinvestigator) will [redacted] prescribe the appropriate study drug on or after the day of the visit following 6 weeks after administration of the appropriate study drug (Visit 5).

[redacted]

(6) Issuance of the drug number of the study drug for the extension period (second prescription in the extension period)

[redacted]

The investigator (or subinvestigator) will [redacted] prescribe the appropriate study drug on or after the day of the visit following 12 weeks after administration of the appropriate study drug (Visit 7).

[redacted]

(7) Issuance of the drug number of the study drug for the extension period (third prescription in the extension period)

[redacted]

[redacted]

The investigator (or subinvestigator) will [redacted] prescribe the appropriate study drug on or after the day of the visit following 24 weeks after administration of the appropriate study drug (Visit 10).

[redacted]

(8) Issuance of the drug number of the study drug for the extension period (fourth prescription in the extension period)

[redacted]

The investigator (or subinvestigator) will [redacted] prescribe the appropriate study drug on or after the day of the visit following 36 weeks after administration of the appropriate study drug (Visit 13).

[redacted]

8.3 Dosage and Administration Method

Two capsules of the randomized study drug will be orally administered once a day every morning for up to 48 weeks. However, the time of administration may be changed only if the investigator (or subinvestigator) judges that it is unavoidable for the treatment of adverse events, etc. (such a change will become effective on or after the following day of the decision). The time of administration may be changed only once per subject (e.g., if morning administration is changed to evening administration, a change from evening administration to morning administration or whatever is not allowed thereafter). The study drug may be taken with or without a meal, and should be taken at the same time of day whenever possible throughout the treatment period.

In subjects randomized to the MT-5199 80 mg group in the double-blind period, the dose should be increased in a blinded manner (40 mg/day in Week 1 and 80 mg/day from Week 2 onwards in the double-blind period). In subjects randomized to the placebo group in the double-blind period and then to the MT-5199 80 mg group in the extension period, the dose should be increased in a blinded manner (40 mg/day in Week 1 and 80 mg/day from Week 2 onwards in the extension period).

The number of capsules to be taken at a time may be changed from two to one if a serious adverse event, important adverse event (see Section 11.2 "Important Adverse Events"), Parkinson-like event, clinically significant laboratory abnormality, etc. are observed after the start of the extension period, and the investigator (or subinvestigator) deems it necessary to ensure the safety of the subjects (however, such a change is not allowed in the double-blind period). The number of capsules to be taken at a time may be changed only once per subject. Also, the number of capsules to be taken at a time may not be changed from one to two. If the sign, symptom, or disease concerned does not tend to improve even after the change, the study treatment should be discontinued. To maintain the study blind, subjects in the placebo group or the MT-5199 40 mg group who undergo such a change will continue receiving the original dose, while those in the MT-5199 80 mg group will receive the study drug at a dose of 40 mg after the change.

(1) Double-blind period (double-blind)

1) Placebo group

Two MT-5199 placebo capsules

2) 40 mg group

One MT-5199 40 mg capsule and one MT-5199 placebo capsule

3) 80 mg group

Two MT-5199 40 mg capsules

However, the dosage from Day 1 to Day 7 should be 40 mg/day (once-daily administration of one MT-5199 40 mg capsule and one MT-5199 placebo capsule).

(2) Extension period (double-blind)

1) 40 mg group

One MT-5199 40 mg capsule and one MT-5199 placebo capsule

2) 80 mg group

Two MT-5199 40 mg capsules

Subjects randomized to the placebo group in the double-blind period and then to the MT-5199 80 mg group in the extension period will receive MT-5199 at a dose of 40 mg/day on Day 1 to Day 7 of the extension period (once-daily administration of one MT-5199 40 mg capsule and one MT-5199 placebo capsule).

[redacted]

[redacted]

[redacted]

8.4 Treatment Period

48 weeks (Double-blind period [double-blind]: 6 weeks, extension period [double-blind]: 42 weeks)

[redacted]

[redacted]

[redacted]

8.5 Concomitant Medications and Therapies

8.5.1 Treatment of Schizophrenia, Schizoaffective Disorder, Bipolar Disorder, or Depressive Disorder, and Extrapyramidal Symptoms, etc.

Treatment of schizophrenia, schizoaffective disorder, bipolar disorder, or depressive disorder, and extrapyramidal symptoms, etc. should be provided as specified below in each period.

(1) From 30 days before the start of the pre-treatment observation period to the start of the pre-treatment observation period

1) The dosage regimen of maintenance therapy drugs for schizophrenia, schizoaffective disorder, bipolar disorder, or depressive disorder, and psychotropic drugs used for extrapyramidal symptoms, etc. (including antiparkinsonian drugs but excluding drugs used as sleeping drugs) should be kept unchanged from at least 30 days before the start of the pre-treatment observation period (or, for benzodiazepines, at least 14 days before the start of the pre-treatment observation period).

2) Benzodiazepines should be used only as maintenance therapy drugs for schizophrenia, schizoaffective disorder, bipolar disorder, or depressive disorder, or as sleeping drugs, and should not be used for other purposes.

3) Among sleeping drugs, the dosage regimen of benzodiazepines should be kept unchanged from at least 14 days before the start of the pre-treatment observation period. Administration of sleeping drugs other than benzodiazepines, including those classified as ultra-short-acting drugs, may be newly started. AIMS examination/assessment should be performed following an interval of at least 8 hours after the use of a sleeping drug, regardless of the type of the sleeping drug used.

(2) From the start of the pre-treatment observation period to the end of the double-blind period

1) Administration of maintenance therapy drugs for schizophrenia, schizoaffective disorder, bipolar disorder, or depressive disorder, and psychotropic drugs used for extrapyramidal symptoms, etc. (including antiparkinsonian drugs but excluding drugs used as sleeping drugs) should be continued without any change in the dosage regimen even after the start of the pre-treatment observation period, and these drugs should not be either discontinued or newly started.

2) Benzodiazepines should be used only as maintenance therapy drugs for schizophrenia, schizoaffective disorder, bipolar disorder, or depressive disorder, or as sleeping drugs, and should not be used for other purposes.

3) Among sleeping drugs, administration of benzodiazepines should be continued without any change in the dosage regimen even after the start of the pre-treatment observation period, and these drugs should not be either discontinued or newly started. Administration of sleeping drugs other than benzodiazepines, including

those classified as ultra-short-acting drugs, may be newly started. AIMS examination/assessment should be performed following an interval of at least 8 hours after the use of a sleeping drug, regardless of the type of the sleeping drug used.

(3) From the extension period to the end of the post-treatment observation period

1) The prescription of maintenance therapy drugs for schizophrenia, schizoaffective disorder, bipolar disorder, or depressive disorder, and psychotropic drugs used for extrapyramidal symptoms, etc. (including antiparkinsonian drugs but excluding drugs used as sleeping drugs) may be modified (including discontinuation and new administration) only if the investigator (or subinvestigator) judges that it is unavoidable for the treatment of adverse events, etc.

2) The prescription of benzodiazepines may be modified (including discontinuation and new administration) only if the investigator (or subinvestigator) judges that it is unavoidable for the treatment of adverse events, etc.

3) The prescription of sleeping drugs may be modified (including discontinuation and new administration) only if the investigator (or subinvestigator) judges that it is unavoidable for the treatment of adverse events, etc. If a sleeping drug is used, however, AIMS examination/assessment should be performed following an interval of at least 8 hours after the use of the sleeping drug.

[redacted]

[redacted]

8.5.2 Prohibited Concomitant Medications and Therapies

It is prohibited to concomitantly use the following medications or therapies during each specified period.

A list of the names (generic names) of the applicable drugs is given in [redacted] "List of Prohibited Concomitant Medications and Sleeping Drugs That Can be Newly Started."

(1) From 90 days before the start of the pre-treatment observation period to the end of the double-blind period

- Botulinum toxin injection

(2) From 30 days before the start of the pre-treatment observation period to the end of the double-blind period (or, for 8) and 10) below, until the end of the extension period)

1) New administration of maintenance therapy drugs for schizophrenia, schizoaffective disorder, bipolar disorder, or depressive disorder, and psychotropic drugs used for extrapyramidal symptoms, etc. (including antiparkinsonian drugs)

- Administration of drugs that have been used without any change in the dosage regimen for at least 30 days before the start of the pre-treatment observation period may be continued.

- Administration of sleeping drugs other than benzodiazepines, including those classified as ultra-short-acting drugs, may be newly started. However, AIMS examination/assessment should be performed following an interval of at least 8 hours after the use of a sleeping drug.

2) New administration of benzodiazepines

- Administration of maintenance therapy drugs for schizophrenia, schizoaffective disorder, bipolar disorder, or depressive disorder, or sleeping drugs that have been used without any change in the dosage regimen from at least 14 days before the start of the pre-treatment observation period may be continued. If a benzodiazepine is used as a sleeping drug, AIMS examination/assessment should be performed following an interval of at least 8 hours after the use of the benzodiazepine.

3) Drugs and foods with potent CYP3A4 inhibitory or inducing action

4) Drugs with potent CYP2D6 inhibitory action

5) Some antiemetics

6) Dopamine receptor stimulants (dopamine agonists)

7) Dopamine precursors

8) MAO inhibitors

9) Central nervous system stimulants

10) VMAT2 inhibitors other than the study drug

11) Deep brain stimulation therapy

12) Supplements and foods containing ginkgo leaf extract

13) Vitamin E preparations and supplements

14) Yi-gan san (yokukan-san)

8.5.3 Recording of Concomitant Medications

The investigator (or subinvestigator) and clinical study collaborators will investigate the drug use status of subjects and record the drug names, and daily dose, and frequency, route, duration, and purpose of administration in the case report form. Investigation and recording should be carried out for the following periods according to the purpose of use of the drug. Recording in the case report form is not necessary for physiological saline used for the purpose of diluting injectable formulations, etc.

(1) Drugs used to treat schizophrenia, schizoaffective disorder, bipolar disorder, or depressive disorder, and extrapyramidal symptoms

- Investigation/recording period: From 90 days before the start of the pre-treatment observation period to the time of the final evaluation

(2) Drugs other than those specified in (1) above

- Investigation/recording period: From the start of the double-blind period to the time of the final evaluation

8.6 Management of Subjects

8.6.1 Instructions for Study Drug Administration

The investigator (or subinvestigator), clinical study collaborators, or study drug manager will instruct subjects regarding study drug administration paying due attention to the following.

(1) Subjects are required to start the study treatment from the following day of the day of first prescription.

(2) Subjects are instructed to take capsules in a blue-colored sheet during Week 1 of both the double-blind period and the extension period.

(3) Subjects are instructed to take two capsules (one row of the sheet) once a day at the same time of day whenever possible, with or without a meal, as directed by the investigator (or subinvestigator). However, subjects should take only one capsule in the right column (within the red frame) if the investigator (or subinvestigator) instructs dose reduction.

(4) In the event that the dose was not taken at the time specified by the investigator (or subinvestigator), subjects should still take it before dinner on the same day (in case of morning administration) or before breakfast on the following day (in case of evening administration at any time other than morning) (however, subjects are prohibited to take the missed dose at a later time than specified above).

(5) On days of visit, subjects are required to take the study drug before the visit. Subjects should bring all study drug supplies (used sheets), whether used or not.

8.6.2 Instructions for Daily Life

The investigator (or subinvestigator) or clinical study collaborators will instruct subjects regarding their daily life paying due attention to the following:

(1) Subjects are required to visit the study site and undergo medical and other examinations on the designated days. Subjects who cannot make the designated visit should contact the investigator (or subinvestigator) or clinical study collaborators and follow instructions given.

(2) Subjects are instructed to carry a study participation card and to present the card when visiting other hospitals or clinical departments. Subjects should notify the investigator

(or subinvestigator) or clinical study collaborators of any drugs/supplements prescribed by physicians other than the investigator (or subinvestigator) of this study or purchased at a pharmacy. Subjects are also required to notify in advance the investigator (or subinvestigator) or clinical study collaborators when starting any additional drugs/supplements during the study.

(3) Subjects are instructed to use the reliable contraceptive measures listed below during the period from the time of informed consent obtainment until 28 days after the completion (discontinuation) of study treatment. Calendar, ovulation, symptothermal, and post-ovulation methods, extravaginal ejaculation, etc. are not acceptable methods of contraception. This, however, does not apply to postmenopausal women with at least 1 year of amenorrhea and those post-surgical for hysterectomy or bilateral oophorectomy.

1) Total abstinence from sexual intercourse

2) Use of two forms of effective contraception. Simultaneous use of a barrier contraceptive (male latex condom or diaphragm pessary) and a more effective form of contraception (oral contraceptive pill, intrauterine device, tubal sterilization, or vasectomy, etc.) is recommended.

(4) In the event that the embryo or fetus of a female subject (or a female partner of a male subject) may have been exposed to the study drug during the contraception period between the time of informed consent obtainment and 28 days after the completion (discontinuation) of study treatment, subjects are required to promptly contact the investigator (or subinvestigator) or a clinical study collaborator.

(5) If any physical abnormalities occur, subjects are required to promptly contact the investigator (or subinvestigator) or a clinical study collaborator and follow their instructions.

(6) Subjects are instructed not to consume grapefruit, grapefruit juice, or processed foods containing any of them during the period from 48 hours before the start of study treatment until the completion (discontinuation) of study treatment.

(7) Subjects are instructed not to donate blood during the period from the time of informed consent obtainment until 4 weeks after the completion (discontinuation) of study treatment.

(8) Subjects are required to exercise sufficient caution when driving a car, riding a motorcycle, or operating dangerous machinery during the period from the start of study treatment until 28 days after the completion (discontinuation) of study treatment.

9 EXAMINATIONS/OBSERVATIONS

9.1 Schedule

• Subjects with schizophrenia or schizoaffective disorder

Examinations/ observations etc.	Informed consent	Pre-treatment observation period		Double-blind period			Extension period											Post-treatment observation period
Visit		Screening (Day −29 to Day −1)	Baseline (Day −8 to Day −1)	W2	W4	W6 [Discontin-uation*2]	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48 [Discontin-uation*2]	Fu4w*1 [Discontin-uation*2 +4w]
Allowable time window (day)				±3	±3	±3[+3]	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7[+3]	+7[+7]
Visit No.	-	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Informed consent	X																	
Subject demographics	X	X																
Inclusion/exclusion criteria	X	X	Update															
Complications		X	Update															
Physical measurements*3		X	(X)*7	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Infection and virus tests		X																
Pregnancy test*4		X	(X)*7	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CYP2D6 genotyping			X															
AIMS [redacted]		X	X	X	X	X			X				X				X	X
CGI-TD						X											X	X
EQ-5D-5L		X				X											X	X
Clinical laboratory tests*5		X	(X)*7	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum prolactin		X	(X)*7	X	X	X	X		X		X		X		X		X	X
Vital signs		X	(X)*7	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead electrocardiogram		X	(X)*7	X	X	X	X	X	X	X	X	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
JCDSS			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SAS			X	X	X	X	X		X		X		X		X		X	X
BARS			X	X	X	X	X		X		X		X		X		X	X
MMSE-J			X			X		X				X					X	
PANSS			X			X			X				X				X	
Drug concentration measurement				X	X	X			X				X				X	X

Examinations/ observations etc.	Informed consent	Pre-treatment observation period		Double-blind period			Extension period										Post-treatment observation period
Visit		Screening (Day −29 to Day −1)	Baseline (Day −8 to Day −1)	W2	W4	W6 [Discontinuation*2]	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48 [Discontinuation*2]	Fu4w*1 [Discontinuation*2 +4w]
Allowable time window (day)				±3	±3	±3[+3]	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7[+3]	+7[+7]
Visit No.	-	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Study drug administration				<═══	═══	═══>	<═══	═══	═══	═══	═══	═══	═══	═══	═══	═══	═══>	
Study drug compliance				X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events				<═══	═══	═══	═══	═══	═══	═══	═══	═══	═══	═══	═══	═══	═══	═══>
Concomitant medications*6	<═══	═══	═══	═══	═══	═══	═══	═══	═══	═══	═══	═══	═══	═══	═══	═══	═══	═══>

*1: 4th week of the post-treatment observation period *2: At the time of discontinuation of study treatment *3: Height and body weight will be measured at screening, and only body weight will be measured at other visits. *4: Only for women of childbearing potential.

*5: HbA1c will be measured only at screening, at baseline, at W6 or at the time of discontinuation in the double-blind period, at W12, W24, W36, and W48 or at the time of discontinuation in the extension period, and at Fu4w or 4 weeks after discontinuation of study treatment.

*6: Drugs used to treat TD, schizophrenia, schizoaffective disorder, bipolar disorder, or depressive disorder, and extrapyramidal symptoms will be investigated for the period from 90 days before the start of the pre-treatment observation period, and drugs used for other purposes will be investigated for the period after baseline.

*7: Screening data may be used as baseline data if the screening test is performed within the allowable time window for the baseline (Day −8 to Day −1).

• Subjects with bipolar disorder or depressive disorder

Examinations/ observations etc.	Informed consent	Pre-treatment observation period		Double-blind period			Extension period											Post-treatment observation period
Visit		Screening (Day −29 to Day −1)	Baseline (Day −8 to Day −1)	W2	W4	W6 [Discontinuation*2]	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48 [Discontinuation*2]	Fu4w*1 [Discontinuation*2 +4w]
Allowable time window (day)				±3	±3	±3[+3]	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7[+3]	+7[+7]
Visit No.	-	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Informed consent	X																	
Subject demographics	X	X																
Inclusion/exclusion criteria	X	X	Update															
Complications		X	Update															
Physical measurements*3		X	(X)*7	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Infection and virus tests		X																
Pregnancy test*4		X	(X)*7	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CYP2D6 genotyping			X															
AIMS [redacted]		X	X	X	X	X			X				X				X	X
CGI-TD						X											X	X
EQ-5D-5L		X				X											X	X
Clinical laboratory tests*5		X	(X)*7	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum prolactin		X	(X)*7	X	X	X	X		X		X		X		X		X	X
Vital signs		X	(X)*7	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead electrocardiogram		X	(X)*7	X	X	X	X	X	X	X	X	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
MADRS-J			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SAS			X	X	X	X	X		X		X		X		X		X	X
BARS			X	X	X	X	X		X		X		X		X		X	X
MMSE-J			X			X		X				X					X	
YMRS			X			X			X				X				X	
Drug concentration measurement				X	X	X			X				X				X	X
Study drug administration				<═══	═══	═══>	<═══	═══	═══	═══	═══	═══	═══	═══	═══	═══	═══>	
Study drug compliance				X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Examinations/ observations etc.	Informed consent	Pre-treatment observation period		Double-blind period			Extension period										Post-treatment observation period
Visit		Screening (Day −29 to Day −1)	Baseline (Day −8 to Day −1)	W2	W4	W6 [Discontin-uation*2]	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48 [Discontin-uation*2]	Fu4w*1 [Discontin-uation*2 +4w]
Allowable time window (day)				±3	±3	±3[+3]	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7[+3]	+7[+7]
Visit No.	-	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Adverse events				<═══	═══	═══	═══	═══	═══	═══	═══	═══	═══	═══	═══	═══	═══	═══>
Concomitant medications*6	<═══	═══	═══	═══	═══	═══	═══	═══	═══	═══	═══	═══	═══	═══	═══	═══	═══	═══>

*1: 4th week of the post-treatment observation period *2: At the time of discontinuation of study treatment *3: Height and body weight will be measured at screening, and only body weight will be measured at other visits. *4: Only for women of childbearing potential.

*5: HbA1c will be measured only at screening, at baseline, at W6 or at the time of discontinuation in the double-blind period, at W12, W24, W36, and W48 or at the time of discontinuation in the extension period, and at Fu4w or 4 weeks after discontinuation of study treatment.

*6: Drugs used to treat TD, schizophrenia, schizoaffective disorder, bipolar disorder, or depressive disorder, and extrapyramidal symptoms will be investigated for the period from 90 days before the start of the pre-treatment observation period, and drugs used for other purposes will be investigated for the period after baseline.

*7: Screening data may be used as baseline data if the screening test is performed within the allowable time window for the baseline (Day −8 to Day −1).

9.2 Items Related to Subject Demographics, etc.

9.2.1 Subject Demographics

Between the time of informed consent obtainment and screening, the investigator (or subinvestigator) will investigate the following subject demographics and record the information in the case report form.

(1) Date of birth

(2) Gender

(3) Race

(4) Type of the underlying disease (schizophrenia, schizoaffective disorder, bipolar disorder, or depressive disorder)

(5) Timing of diagnosis of the underlying disease

(6) Timing of diagnosis of TD

(7) Childbearing potential (female subjects only)

* As a rough guide, women who have had no menstruation for at least 1 year or undergone surgical hysterectomy or bilateral oophorectomy are judged to be of no childbearing potential.

9.2.2 Inclusion/Exclusion Criteria

Between the time of informed consent obtainment and baseline (before initial randomization), the investigator (or subinvestigator) will check the subjects' compliance with the inclusion and exclusion criteria and record the information in the case report form.

9.2.3 Complications

Between the time of informed consent obtainment and baseline (before initial randomization), the investigator (or subinvestigator) will investigate the subjects' complications and record the complications at baseline (before initial randomization) in the case report form.

9.2.4 Physical Measurements

The investigator (or subinvestigator) will measure height and body weight at screening and body weight at baseline, at Week 2, Week 4, and Week 6 or at the time of discontinuation in the double-blind period, at Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32,

Week 36, Week 40, Week 44, and Week 48 or at the time of discontinuation in the extension period, and at the 4th week of the post-treatment observation period or 4 weeks after discontinuation of study treatment, and record the measurement results in the case report form. Screening data will be used as baseline data if the screening test is performed within the allowable time window for the baseline (Day −8 to Day −1).

9.2.5 Infection and Virus Tests

The investigator (or subinvestigator) will perform blood sampling for infection and virus tests at screening and record the date of blood sampling in the case report form. About 8 mL of blood will be sampled at a time. The samples will be collected and measured by the contract clinical laboratory.

9.2.6 Pregnancy Test (Only for Women of Childbearing Potential)

For female subjects of childbearing potential, the investigator (or subinvestigator) will perform a urine HCG test at each study site at screening, at baseline, at Week 2, Week 4, and Week 6 or at the time of discontinuation in the double-blind period, at Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, and Week 48 or at the time of discontinuation in the extension period, and at the 4th week of the post-treatment observation period or 4 weeks after discontinuation of study treatment. For the volume of urine to be sampled at a time, the regulations of each study site should be followed. Screening data may be used as baseline data if the screening test is performed within the allowable time window for the baseline (Day −8 to Day −1).

9.2.7 CYP2D6 Genotyping

The investigator (or subinvestigator) will perform blood sampling for CYP2D6 genotyping at baseline. [redacted] the samples will be collected and measured by the contract clinical laboratory.

The contract clinical laboratory will not report the results of measurement to the sponsor or study sites until the key code is unblinded.

9.2.8 Date of Initial Randomization and Study Drug Compliance

The investigator (or subinvestigator) will record the date of initial randomization and the drug numbers of the study drug for the double-blind period and the study drug for the extension period (including the drug numbers of study drugs that were issued but not prescribed) in the case report form. If the dose is reduced, the start date of dose reduction and the reason for dose reduction will be recorded in the case report form.

9.2.9 Study Drug Compliance

The investigator (or subinvestigator) will investigate and record the start and end dates of administration of the study drug for the double-blind period and the study drug for the extension period in the case report form. In addition, the number of study drugs prescribed, the number of study drugs collected, and the number of days on which the subject failed to take the study drug will be investigated at each visit after the start of study treatment, and recorded in the case report form. Also, at the specified blood sampling time points for drug concentration measurement, the date and time of the last dose of the study drug will be investigated and recorded in the case report form.

9.2.10 Status of Change in the Time of Study Drug Administration

If the investigator (or subinvestigator) changes the time of administration of the study drug for the double-blind period or the study drug for the extension period, he/she will record the date of change, the time of administration after the change, and the reason for the change in the case report form.

9.3 Efficacy Endpoints

9.3.1 AIMS

AIMS examination/assessment at scheduled visits will be performed following an interval of at least 8 hours after the use of a sleeping drug. AIMS examination/assessment will be performed at the same time of day throughout the study period.

(1) Central assessment

The investigator (or subinvestigator) will perform [redacted] the procedure separately specified by the sponsor at screening, at baseline, at Week 2, Week 4, and Week 6 or at the time of discontinuation in the double-blind period, at Week 16, Week 32, and Week 48 or at the time of discontinuation in the extension period, and at the 4th week of the post-treatment observation period or 4 weeks after discontinuation of study treatment, and send the recorded data to the central AIMS assessment facility. [redacted]

(2) Assessment by the investigator (or subinvestigator)

The investigator (or subinvestigator) will assess AIMS Items 1 to 12 ([redacted] see Section 10 "Methods and Criteria for Evaluation") at screening, at baseline, at Week 2, Week 4, and Week 6 or at the time of discontinuation in the double-blind period, at Week 16, Week 32, and Week 48 or at the time of discontinuation in the extension

period, and at the 4th week of the post-treatment observation period or 4 weeks after discontinuation of study treatment, and record the information in the case report form.

9.3.2 CGI-TD

The investigator (or subinvestigator) will assess CGI-TD ([redacted] see Section 10 "Methods and Criteria for Evaluation") at Week 6 or at the time of discontinuation in the double-blind period, at Week 48 or at the time of discontinuation in the extension period, and at the 4th week of the post-treatment observation period or 4 weeks after discontinuation of study treatment, and record the information in the case report form.

9.3.3 EQ-5D-5L

The investigator (or subinvestigator) will have subjects fill out an EQ-5D-5L questionnaire ([redacted] see Section 10 "Methods and Criteria for Evaluation") at screening, at Week 6 or at the time of discontinuation in the double-blind period, at Week 48 or at the time of discontinuation in the extension period, and at the 4th week of the post-treatment observation period or 4 weeks after discontinuation of study treatment, and record the information in the case report form.

9.4 Safety Endpoints

9.4.1 Clinical Laboratory Tests

The investigator (or subinvestigator) will perform blood and urine sampling for clinical laboratory tests at screening, at baseline, at Week 2, Week 4, and Week 6 or at the time of discontinuation in the double-blind period, at Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, and Week 48 or at the time of discontinuation in the extension period, and at the 4th week of the post-treatment observation period or 4 weeks after discontinuation of study treatment, and record the date of blood sampling and the food intake status at the time of blood sampling (fasted or fed) in the case report form. About 8 to 12 mL of blood and about 5 mL of urine will be sampled at a time. The samples will be collected and measured by the contract clinical laboratory. Screening data may be used as baseline data if the screening test is performed within the allowable time window for the baseline (Day −8 to Day −1).

The test items are as follows. HbA1c will be measured only at screening, at baseline, at Week 6 or at the time of discontinuation in the double-blind period, at Week 12, Week 24, Week 36, and Week 48 or at the time of discontinuation in the extension period, and at the 4th week of the post-treatment observation period or 4 weeks after discontinuation of study treatment. If the ALT or AST level exceeds 3 times the upper limit of normal (ULN), PT-INR will also be measured and the need for discontinuation of study treatment will be determined in light of Section 12.1 "Criteria for Discontinuation of Study Treatment."

(1) Hematology

White blood cell count, white blood cell fraction (neutrophils, lymphocytes, monocytes, eosinophils, basophils), red blood cell count, hemoglobin, hematocrit, platelet count

(2) Serum biochemistry

Total protein, albumin, AST, ALT, LDH, total bilirubin, direct bilirubin, indirect bilirubin, ALP, γ-GTP, CPK, urea nitrogen, serum creatinine, uric acid, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglyceride, glucose, HbA1c, Na, K, Cl

(3) Urinalysis (qualitative)

Glucose, protein, occult blood

9.4.2 Serum Prolactin

The investigator (or subinvestigator) will perform blood sampling for the serum prolactin test at screening, at baseline, at Week 2, Week 4, and Week 6 or at the time of discontinuation in the double-blind period, at Week 8, Week 16, Week 24, Week 32, Week 40, and Week 48 or at the time of discontinuation in the extension period, and at the 4th week of the post-treatment observation period or 4 weeks after discontinuation of study treatment (see Section 9.4.1 "Clinical Laboratory Tests" for the volume of blood to be sampled). The samples will be collected and measured by the contract clinical laboratory. Screening data may be used as baseline data if the screening test is performed within the allowable time window for the baseline (Day −8 to Day −1).

The contract clinical laboratory will not report the results of serum prolactin measurement after the start of study treatment to the sponsor or study sites until the key code is unblinded. Serum prolactin measurement outside the contract clinical laboratory is prohibited during the period from the start of study treatment until the end of the study period.

9.4.3 Vital Signs

The investigator (or subinvestigator) will measure blood pressure (systolic and diastolic), pulse rate, and axillary temperature (in degrees Celsius, to one decimal place) at screening, at baseline, at Week 2, Week 4, and Week 6 or at the time of discontinuation in the double-blind period, at Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, and Week 48 or at the time of discontinuation in the extension period, and at the 4th week of the post-treatment observation period or 4 weeks after discontinuation of study treatment, and record the results in the case report form. Vital signs should be measured in the sitting position after confirming that the subject has been at rest for at least 5 minutes. Screening data may be used as baseline data if the screening test is performed within the

allowable time window for the baseline (Day −8 to Day −1).

9.4.4 12-lead Electrocardiogram

The investigator (or subinvestigator) will perform 12-lead ECG at screening, at baseline, at Week 2, Week 4, and Week 6 or at the time of discontinuation in the double-blind period, at Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, and Week 48 or at the time of discontinuation in the extension period, and at the 4th week of the post-treatment observation period or 4 weeks after discontinuation of study treatment, and record the QT, QRS, PR interval, RR interval, HR, and the presence or absence of abnormal findings in the case report form. The 12-lead ECG should be performed after confirming that the subject has been at rest for at least 5 minutes. Screening data may be used as baseline data if the screening test is performed within the allowable time window for the baseline (Day −8 to Day −1).

9.4.5 C-SSRS

The investigator (or subinvestigator) will assess C-SSRS ([redacted] see Section 10 "Methods and Criteria for Evaluation") at baseline, at Week 2, Week 4, and Week 6 or at the time of discontinuation in the double-blind period, at Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, and Week 48 or at the time of discontinuation in the extension period, and at the 4th week of the post-treatment observation period or 4 weeks after discontinuation of study treatment, and record the information in the case report form.

9.4.6 SAS

The investigator (or subinvestigator) will assess SAS ([redacted] see Section 10 "Methods and Criteria for Evaluation") at baseline, at Week 2, Week 4, and Week 6 or at the time of discontinuation in the double-blind period, at Week 8, Week 16, Week 24, Week 32, Week 40, and Week 48 or at the time of discontinuation in the extension period, and at the 4th week of the post-treatment observation period or 4 weeks after discontinuation of study treatment, and record the information in the case report form.

9.4.7 BARS

The investigator (or subinvestigator) will assess BARS ([redacted] see Section 10 "Methods and Criteria for Evaluation") at baseline, at Week 2, Week 4, and Week 6 or at the time of discontinuation in the double-blind period, at Week 8, Week 16, Week 24, Week 32, Week 40, and Week 48 or at the time of discontinuation in the extension period, and at the 4th week of the post-treatment observation period or 4 weeks after discontinuation of study treatment, and

record the information in the case report form.

9.4.8 MMSE-J

The investigator (or subinvestigator) will assess MMSE-J ([redacted] see Section 10 "Methods and Criteria for Evaluation") at baseline, at Week 6 or at the time of discontinuation in the double-blind period, and at Week 12, Week 28, and Week 48 or at the time of discontinuation in the extension period, and record the information in the case report form.

9.4.9 JCDSS

JCDSS assessment will be performed if the subject's underlying disease is schizophrenia or schizoaffective disorder.

The investigator (or subinvestigator) will assess JCDSS ([redacted] see Section 10 "Methods and Criteria for Evaluation") at baseline, at Week 2, Week 4, and Week 6 or at the time of discontinuation in the double-blind period, at Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, and Week 48 or at the time of discontinuation in the extension period, and at the 4th week of the post-treatment observation period or 4 weeks after discontinuation of study treatment, and record the information in the case report form.

9.4.10 PANSS

PANSS assessment will be performed if the subject's underlying disease is schizophrenia or schizoaffective disorder.

The investigator (or subinvestigator) will assess PANSS ([redacted] see Section 10 "Methods and Criteria for Evaluation") at baseline, at Week 6 or at the time of discontinuation in the double-blind period, and at Week 16, Week 32, and Week 48 or at the time of discontinuation in the extension period, and record the information in the case report form.

9.4.11 MADRS-J

MADRS-J assessment will be performed if the subject's underlying disease is bipolar disorder or depressive disorder.

The investigator (or subinvestigator) will assess MADRS-J ([redacted] see Section 10 "Methods and Criteria for Evaluation") at baseline, at Week 2, Week 4, and Week 6 or at the time of discontinuation in the double-blind period, at Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, and Week 48 or at the time of discontinuation in the extension period, and at the 4th week of the post-treatment observation

period or 4 weeks after discontinuation of study treatment, and record the information in the case report form.

9.4.12 YMRS

YMRS assessment will be performed if the subject's underlying disease is bipolar disorder or depressive disorder.

The investigator (or subinvestigator) will assess YMRS ([redacted] see Section 10 "Methods and Criteria for Evaluation") at baseline, at Week 6 or at the time of discontinuation in the double-blind period, and at Week 16, Week 32, and Week 48 or at the time of discontinuation in the extension period, and record the information in the case report form.

9.4.13 Adverse Events

The investigator (or subinvestigator) will confirm the presence or absence of adverse events through examinations, etc. (see Section 10 "Methods and Criteria for Evaluation") and record the information in source documents such as medical records.

The investigator (or subinvestigator) will record the adverse event term, date of onset, severity, seriousness, causal relationship to the study drug, outcome, date of outcome, action taken for the study drug, and other actions taken in the case report form.

9.5 Pharmacokinetic Endpoints

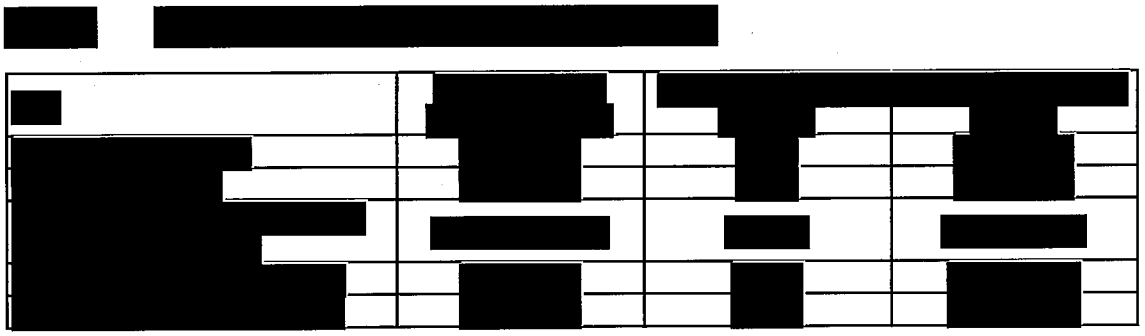
The investigator (or subinvestigator) will perform blood sampling for drug concentration measurement at Week 2, Week 4, and Week 6 or at the time of discontinuation in the double-blind period, at Week 16, Week 32, and Week 48 or at the time of discontinuation in the extension period, and at the 4th week of the post-treatment observation period or 4 weeks after discontinuation of study treatment, and record the date and time of blood sampling in the case report form. [redacted] The samples will be collected and measured by the contract clinical laboratory and the drug concentration measurement facility, respectively.

[redacted]

The drug concentration measurement facility will not report the results of drug concentration measurement to the sponsor or study sites until the key code is unblinded.

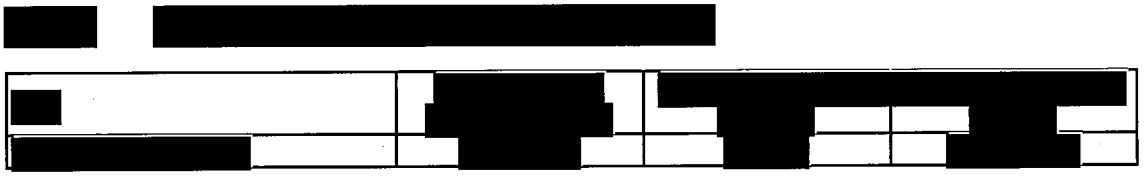
9.6 Volume of Blood Sampled

[redacted]



9.7 Volume of Urine Sampled

[redacted]



10 METHODS AND CRITERIA FOR EVALUATION

10.1 Efficacy

10.1.1 AIMS

The AIMS [redacted] is a measure to assess abnormal involuntary movements and is mainly used for TD assessment[4]. It consisted of body part-specific severity assessment in muscles of facial expression, lips and perioral area, jaw, tongue, upper extremities, lower extremities, and trunk (Items 1 to 7), global assessment (Items 8 to 10), and two questions about the dental status (Items 11 and 12). The body part-specific severity assessment and global assessment are carried out on a 5-point scale ranging from 0 "none" to 4 "severe."

[redacted] In the central assessment at screening, a physician skilled in the diagnosis and assessment of TD will check the severity of TD and the presence or absence of coexisting abnormal involuntary movements such as dystonia, akathisia, and parkinsonism to determine the eligibility of subjects. In the central assessment after baseline, two physicians skilled in the diagnosis and assessment of TD will work together to assess Items 1 to 7 in a blinded manner after randomizing the evaluation time points [redacted]. For the severity of each item, the result agreed upon by the two raters will be adopted.

Assessment (Items 1 to 12) will also be performed by the investigator (or subinvestigator) as a secondary endpoint.

The rater of central assessment and the investigator (or subinvestigator) will assess Items 1 to 7 in accordance with the criteria in Table 3.

Table 3 Criteria for AIMS Assessment (Items 1 to 7)

Score	Assessment criteria for Items 1 to 7
0	None: No dyskinesia
1	Minimal or slight dyskinesia: Low amplitude, present during some but not most of the exam
2	Mild dyskinesia: Low amplitude and present during most of the exam (or moderate amplitude and present during some of exam)
3	Moderate dyskinesia: Moderate amplitude and present during most of exam
4	Severe dyskinesia: Maximal amplitude and present during most of exam

10.1.2 CGI-TD

The CGI-TD [redacted] is a measure to assess the clinical global impression of change in TD symptoms from baseline on a 7-point scale ranging from 1 "very much improved" to 7 "very much worse."

10.1.3 EQ-5D-5L

The EQ-5D-5L [redacted] is a questionnaire for exploratory assessment of the effect of MT-5199 administration on the QOL of subjects. The questionnaire consists of five questions, each of which is answered by the subject according to five levels.

10.2 Safety

10.2.1 Adverse Events

An adverse event is defined as any clinically untoward or unintended sign (including a clinically significant abnormal laboratory test finding), symptom, or disease that occurred during the period from the start of the study treatment until the 4th week of the post-treatment observation period or 4 weeks after discontinuation of study treatment regardless of causal relationship to the study drug.

Clinically significant abnormal laboratory test findings will be determined in accordance with the following criteria. However, if the abnormal laboratory test finding is already included in a separately reported sign, symptom, or disease, it does not need to be handled as a discrete adverse event.

- The method of study drug administration was changed (dose reduction or discontinuation) due to the abnormal laboratory test finding.
- Treatment other than the study drug was necessary due to the abnormal laboratory test finding.
- Surgical intervention was necessary due to the abnormal laboratory test finding.
- The abnormal laboratory test finding meets the definition of serious adverse events.
- The abnormal laboratory test finding is of clinical concern as judged by a physician.

The investigator (or subinvestigator) will handle any of the above signs, symptoms, and diseases as adverse events if they occur after the start of study treatment.

(1) Adverse event term

For terms used for adverse event reporting, the following rules should be followed.

- In principle, the diagnosis should be used.
- If the diagnosis is not definite, the symptom name may be used.
- If more than one symptom is present and they can be represented by a single diagnosis, the diagnosis should be used.
- Surgical treatment, etc. should not be handled as an adverse event. Instead, if a disease or symptom requiring surgical treatment, etc., has been identified, the disease or symptom should be handled as an adverse event.

(2) Date of onset

Date of onset is defined as the day when the relevant symptom is observed or the day of examination when the relevant laboratory abnormality is identified.

(3) Severity

The severity of adverse events will be categorized as follows:

1. Mild: Does not interfere with the activities of daily living of subjects.
2. Moderate: Interferes with the activities of daily living of subjects to a certain extent.
3. Severe: Substantially interferes with the activities of daily living of subjects.

(4) Seriousness

The seriousness of adverse events will be categorized as follows:

1. Not serious: other than 2.
2. Serious: a to f below
    a. Adverse events that result in death
    b. An adverse event that is life-threatening (The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
    c. Adverse events that require inpatient hospitalization or prolongation of existing hospitalization (excluding hospitalization for management or social or personal reasons)
    d. Adverse events that result in persistent or significant disability/incapacity (essential destruction of the ability to perform normal vital functions)
    e. Adverse events that are congenital anomalies/birth defects

f. Other events or reactions considered medically important conditions (Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as "important medical events" that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the patient or might require intervention or treatment to prevent one of the other outcomes listed in the definition above. Examples of such events include intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse).

(5) Causal relationship to the study drug

The investigator (or subinvestigator) will assess "reasonable possibility" that the study drug may cause the relevant adverse event in consideration of the natural course of the underlying diseases such as primary disease and complications, concomitant therapy, possible causes other than the study drug such as other risk factors, and temporal relationship between the study drug and the onset of the adverse event (e.g., relapse after rechallenge and disappearance after withdrawal from the study drug). Adverse events assessed to be related to the study drug with a "reasonable possibility" will be handled as adverse drug reactions.

1. Reasonable possibility
2. No reasonable possibility

(6) Outcome

The outcome of adverse events will be classified into the following 6 categories:

1. Resolved
2. Resolving
3. Not resolved
4. Resolved with sequelae
5. Fatal
6. Unknown

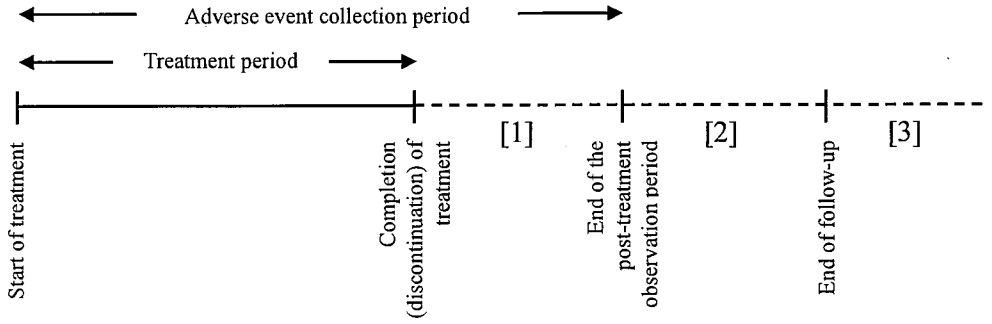
(7) Date of outcome

The date of outcome will be categorized as follows:

1. Resolved	:	Date when the relevant adverse event has resolved. If the resolution date is unclear, the date when the outcome is confirmed or determined will be referred to as the date of outcome.
2. Resolving	:	Date when the relevant adverse event is confirmed or determined to be resolving.
3. Not resolved	:	Date when the relevant adverse event is confirmed or determined not to be resolved.
4. Resolved with sequelae	:	Date when the adverse event is confirmed or determined to be accompanied by any sequelae.
5. Fatal	:	Date when the subject died. If the date of death cannot be identified, the date when death is confirmed or determined is referred to as the date of death.
6. Unknown	:	Date when the subject died if the outcome is unknown because the subject died due to causes other than the relevant adverse event. In other cases, the date when the outcome is confirmed or determined is referred to as the date of outcome.

(8) Adverse event collection period and follow-up

Information on adverse events that occur during the period from the start of study treatment until the 4th week of the post-treatment observation period or 4 weeks after discontinuation of study treatment will be collected. For adverse events of which the outcome is other than "resolved," "resolved with sequelae," or "fatal" at the 4th week of the post-treatment observation period or 4 weeks after discontinuation of study treatment and which are assessed to be related to the study drug with a "reasonable possibility," 28-day follow-up will be performed. If no resolution is observed as a result of follow-up, the outcome on the last day of follow-up and the date of outcome will be recorded in the case report form, and investigation of the course will be continued thereafter. If follow-up of adverse drug reactions with an outcome other than "resolved," "resolved with sequelae," or "fatal" is discontinued, the reason will be recorded in source documents such as medical records.



- The duration of Period [1] is 28 days, and the presence or absence of adverse events will be investigated. (Period [1] continues until the day on which all assessments and examinations in the post-treatment observation period are completed)

- The duration of Period [2] following the post-treatment observation period is 28 days, and adverse events that occur during the treatment period and Period [1] of which the outcome is other than "resolved," "resolved with sequelae," or "fatal" and which are assessed to be related to the study drug with a "reasonable possibility" will be followed in Period [2].

- The course of adverse events followed in Period [2] will be recorded in the case report form.

- For adverse events of which the outcome at the end of Period [2] is other than "resolved," "resolved with sequelae," or "fatal" and which are assessed to be related to the study drug with a "reasonable possibility," the date of last observation in Period [2] will be recorded as the date of outcome in the case report form.

- For adverse events of which the outcome at the end of Period [2] is other than "resolved," "resolved with sequelae," or "fatal" and which are assessed to be related to the study drug with a "reasonable possibility," the subsequent course (Period [3]) will be followed.

- If there is a justifiable reason to discontinue follow-up after the end of Period [1], the reason will be recorded in source documents such as medical records, and follow-up will then be terminated.

10.2.2 C-SSRS

The C-SSRS [redacted] is a scale to assess the severity of suicidal ideation and suicide attempts[7]. Suicidal ideation is classified into five categories: 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), and 5 (active suicidal ideation with specific plan and intent), and the frequency, duration, controllability, deterrents, and reasons for occurrence are assessed with respect to the most severe type of ideation. Suicidal behaviors are categorized as actual attempts, interrupted

attempts, aborted attempts, and other preparatory acts, and the actual lethality or potential lethality are assessed for each of the initial attempt, the most lethal attempt, and the most recent attempt.

10.2.3 SAS

The SAS [redacted] is a scale to assess extrapyramidal symptoms[8]. Ten items consisting of gait, arm dropping, shoulder shaking, elbow rigidity, fixation of position or wrist rigidity, leg pendulousness, head dropping, glabella tap, tremor, and salivation are assessed on a 5-point scale ranging from 0 "none" to 4 "severe."

10.2.4 BARS

The BARS [redacted] is a scale to assess drug-induced akathisia[9), 10]. Three items consisting of objective symptoms of akathisia, subjective symptoms of akathisia, and distress related to subjective symptoms of akathisia are assessed on a 4-point scale ranging from 0 to 3. Global clinical assessment of akathisia is also performed on a 6-point scale ranging from 0 (none) to 5 (severe).

10.2.5 MMSE-J

The MMSE-J [redacted] is a measure to assess cognitive function[11), 12]. It consists of 11 items to assess cognitive functions such as orientation, memory, attention and calculation, language function, verbal command action, and graphic drawing. The first five questions test linguistic ability, and the remaining six questions test mobility.

10.2.6 JCDSS

The JCDSS [redacted] is a scale to assess the severity of depressive symptoms in patients with schizophrenia[13), 14), 15]. A total of nine items, consisting of eight items related to subjective symptoms and one item related to objective symptoms based on observation, are assessed on a 4-point scale ranging from 0 "none" to 3 "severe."

In this study, JCDSS assessment will be performed only in subjects with schizophrenia or schizoaffective disorder as the underlying disease.

10.2.7 PANSS

The PANSS [redacted] is a scale to assess positive and negative symptoms in patients with schizophrenia[16), 17]. A total of 30 items, consisting of seven items on a positive symptom

scale, seven items on a negative symptom scale, and 16 items on a global psychiatric symptom scale, are assessed on a 7-point scale ranging from 1 "none" to 7 "most severe."

In this study, PANSS assessment will be performed only in subjects with schizophrenia or schizoaffective disorder as the underlying disease.

10.2.8 MADRS-J

The MADRS-J [redacted] is a scale to assess the severity of depressive symptoms[18), 19), 20)]. Ten items related to depressive symptoms are assessed in increments of two anchor points on a 7-point scale ranging from 0 to 6.

In this study, MADRS-J assessment will be performed only in subjects with bipolar disorder or depressive disorder as the underlying disease.

10.2.9 YMRS

The YMRS [redacted] is a scale to assess the severity of manic symptoms[21), 22)]. Eleven items consisting of elevated mood, increased motor activity-energy, sexual interest, sleep, irritability, speech (rate and amount), language-thought disorder, thought content, disruptive-aggressive behavior, appearance, and insight are assessed on a 5-point scale ranging. The scores for the four items of irritability, speech, thought content, and disruptive-aggressive behavior are weighted twice as much as the other seven items to compensate for cases where severe manic symptoms prevent interviews. That is, the score for each item is 0 to 4 or 0 to 8, and the total score ranges from 0 to 60.

In this study, YMRS assessment will be performed only in subjects with bipolar disorder or depressive disorder as the underlying disease.

11 SUBJECT'S SAFETY ASSURANCE

11.1 Action to Be Taken in the Event of Serious Adverse Events

If a serious adverse event occurs during the period from the start of study treatment until the 4th week of the post-treatment observation period or 4 weeks after discontinuation of study treatment, the investigator (or subinvestigator) will promptly take appropriate measures on the subject, regardless whether the event is related to the study drug or not.

The investigator (or subinvestigator) will promptly report the occurrence of the serious adverse event (in written form in principle) to the sponsor and provide the sponsor with detailed written information, including the causal relationship to the study drug, within 7 days after reporting. The investigator will also report the serious adverse event to the head of the study site.

The following is the relationship between the definition of serious adverse events in Section 10 "Methods and Criteria for Evaluation" ("Seriousness" Criteria in the ICH, PAB/PCD Notification No. 227) and the definition of serious adverse events described in Article 273 of the Regulation for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices.

10. Methods and Criteria for Evaluation ("Seriousness" Criteria in the ICH, PAB/PCD Notification No. 227)		Article 273 of the Regulation for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices
Adverse events that result in death	↔	Death
An adverse event that is life-threatening	↔	A case which may lead to death
Adverse events that require inpatient hospitalization or prolongation of existing hospitalization	↔	A case which requires hospitalization in a hospital or clinic or extension of a hospitalization period for treatment
Adverse events that result in persistent or significant disability/incapacity	↔	Disability
Other events or reactions considered medically important conditions	↔	A case which may lead to disability
	↔	A case of a serious disease according to the above cases
Adverse events that are congenital anomalies/birth defects	↔	A congenital disease or abnormality in later generations

11.2 Important Adverse Events

Suicidal ideation and suicide attempt are defined as important adverse events for investigation of the safety profile of MT-5199. If any of these adverse events occur, the investigator (or subinvestigator) will promptly report the situation to the sponsor.

With regard to suicidal ideation, suicidal attempt, depression, and depressive state, the sponsor will periodically assess the occurrence status and incidence to determine whether the study should be continued and whether changes to the protocol are necessary, etc.

11.3 Pregnancy Report

If the investigator becomes aware of the possibility that the embryo or fetus of a female subject (or a female partner of a male subject) may have been exposed to the study drug during the period between the start of study treatment and 28 days after the completion (discontinuation) of study treatment, the investigator will immediately report to the sponsor by using the form provided [redacted]. If the female subject (or the female partner of the male subject) intends to give birth, the investigator will follow the subject to the extent possible until delivery to investigate whether there is any effect of the study drug on the offspring, and report the results to the sponsor by using the form provided [redacted].

11.4 Contacting Other Physicians Treating Subjects etc.

The investigator (or subinvestigator) will check whether subjects are consulting a physician other than the investigator of this study when obtaining informed consent and during the study period. If the subject is being examined by another physician, the relevant physician will be notified of the subject's participation in the study with the subject's consent. The investigator (or subinvestigator) or a clinical study collaborator will issue a clinical study participation card to have other physicians informed of the subject's participation in the study via the subject and instruct the subject to present the card when the subject visits other hospitals or clinical departments.

12 CRITERIA AND PROCEDURES FOR WITHDRAWAL OF SUBJECTS

12.1 Criteria for Discontinuation of Study Treatment

If any of the following criteria are met, the investigator (or subinvestigator) will discontinue the study treatment for the relevant subject.

(1) Upon request from the subject to discontinue participation in the study

(2) If the investigator (or subinvestigator) decides it not appropriate to continue the study treatment due to exacerbation of the underlying disease

(3) If the investigator (or subinvestigator) decides it difficult to continue the study treatment for the subject due to an adverse event, etc.

(4) If C-SSRS assessment indicates a suicide attempt or suicidal ideation corresponding to Item 4 or 5.

(5) If any of the following laboratory abnormalities (and adverse events) are observed.

1) Liver function test values

- ALT or AST >8×ULN
- ALT or AST >5×ULN for 2 weeks or longer
- ALT or AST >3×ULN, AND total bilirubin >2×ULN or PT-INR >1.5
- ALT or AST >3×ULN, AND occurrence of fatigue, nausea, vomiting, right upper abdominal pain/tenderness, fever, rash, or eosinophilia (> 5%)

2) Serum creatinine

- Subjects with a baseline serum creatinine level not exceeding the ULN
  - Serum creatinine >1.5×baseline level, AND serum creatinine >ULN for 2 weeks or longer
- Subjects with a baseline serum creatinine level exceeding the ULN
  - Serum creatinine >1.5×baseline level for 2 weeks or longer

(6) If QTcF is 500 msec or more, or a clinically significant abnormality is observed on 12-lead ECG

(7) If it is found that the continuation of the study is not feasible due to the subject's circumstances, etc.

(8) If it is found that the subject is pregnant

(9) If the sponsor notifies that the study treatment should be discontinued

(10) Other cases where the investigator (or subinvestigator) decides that the study treatment for the subject should be discontinued

[redacted]

12.2 Criteria for Study Discontinuation

If any of the following criteria are met, the investigator (or subinvestigator) will discontinue the study for the relevant subject.

(1) Upon request from the subject to discontinue participation in the study

(2) If it is found that the continuation of the study is not feasible due to the subject's circumstances, etc.

(3) If the sponsor notifies that the study should be discontinued

(4) Other cases where the investigator (or subinvestigator) decides the study for the subject should be discontinued

[redacted]

12.3 Procedures for Withdrawal of Subjects

In the event of discontinuation of study treatment or the study, the investigator (or subinvestigator) will take appropriate measures for the subject and perform the specified tests and observations according to the timing of discontinuation. The investigator (or subinvestigator) will also promptly inform the sponsor of the discontinuation. [redacted] The date of discontinuation is defined as the date when the investigator (or subinvestigator) has decided the discontinuation.

If the study treatment is discontinued, the tests and observations specified at the time of discontinuation will be performed within 3 days after the day of discontinuation. In addition, the tests and observations specified at the time of post-treatment observation will be performed at 4 weeks after discontinuation of treatment.

If it is decided to discontinue the study treatment and the study on the same day, the tests and observations specified at the time of discontinuation of study treatment will be performed within 3 days after the date of study discontinuation whenever possible. If the study is discontinued before the start of study treatment, no tests or observations are necessary.

Tests and observations associated with discontinuation of study treatment should be performed as much as possible, even if they cannot be performed within the above period.

For subjects who were unable to undergo the tests and observations or who failed to visit the study site after discontinuation, follow-up investigation will be performed in writing (letter) or by telephone, etc. regarding the reasons and subsequent course, etc.

The investigator (or subinvestigator) will record the date of and reason for discontinuation in the case report form. The reason for discontinuation of study treatment should be selected from among those described in Section 12.1 "Criteria for Discontinuation of Study Treatment," together with one of the following reasons: adverse events, death, loss to follow-up, physician's judgment, pregnancy, exacerbation of the underlying disease, sponsor's decision of discontinuation, subject's wish for discontinuation, and others.

13 STATISTICAL ANALYSIS

In this protocol, the description of the statistical method is minimized to the utmost. More detailed technical statistical method will be described in the statistical analysis plan to be prepared separately by the time of data lock.

13.1 Analysis Sets

(1) Safety analysis set

The safety analysis set will consist of subjects who satisfy both of the following conditions.

- Subjects who were randomized and took the study drug
- Subjects for whom post-baseline safety data are available

(2) Intent-to-Treat (ITT) analysis set

The ITT analysis set will consist of subjects who satisfy all of the following conditions.

- Subjects in the safety analysis set
- Subjects for whom the baseline AIMS total score (Items 1 to 7; central assessment [redacted]) is available
- Subjects for whom at least one AIMS total score (Items 1 to 7; central assessment [redacted]) after baseline in the double-blind period is available

(3) Per-Protocol (PP) analysis set

The PP analysis set will consist of subjects who satisfy all of the following conditions.

- Subjects in the ITT analysis set
- Subjects for whom the AIMS total score (Items 1 to 7; central assessment [redacted]) at Week 6 is available
- Subjects without significant protocol deviations related to efficacy
- Subjects who were randomized to an active treatment group in the double-blind period and in whom the plasma concentration of unchanged drug (MT-5199) at Week 6 was detectable

(4) Pharmacokinetic analysis set

The pharmacokinetic analysis set is an analysis population consisting of randomized

subjects, excluding the following subjects:

- Subjects who did not take the study drug at all
- Subjects with no drug concentration data after study drug administration

13.2 Data Handling

Tabulation of data at each measurement time point will be performed at the time points defined in Section 9.1 for each item. However, the time of discontinuation of study treatment will not be handled as a time point for data tabulation.

In the tabulation of data at each measurement time point, data within the allowable time window defined in Section 9.1 "Schedule" will be adopted from among all measurement data. However, if measurement is impossible or only yields a reference value due to a missing test or a problem with the laboratory sample, etc., the data should be handled as missing data and should not be adopted. If there are adoptable data at more than one time point in the allowable time window, the data obtained at the time point closer to the day of the scheduled visit should be adopted. If data are available at two different time points that are equally close to the day of the scheduled visit, the data obtained later should be adopted.

13.3 Planned Analyses

13.3.1 Efficacy Endpoints

Analyses will be performed using the ITT analysis set.

(1) Double-blind period

1) Primary efficacy endpoint

- Change from baseline in the AIMS total score (Items 1 to 7; central assessment [redacted]) at Week 6

(a) Primary analysis

Each of the MT-5199 groups (40 mg group and 80 mg group) will be compared with the placebo group by means of an analysis using the mixed-effect model repeated measures (MMRM), with group, underlying disease, and time point as fixed effects, baseline as a covariate, and group × evaluation time point and baseline × evaluation time point as interactions. The variance-covariance matrix of within-subject scores will be unstructured, and the degree of freedom will be calculated by the method of Kenward and Roger (1997). Missing values will not be imputed.

The following fixed-sequence procedure will be followed to control the type I

family-wise error rate in the comparison between each of the MT-5199 groups and the placebo group.

- Step 1: The 80 mg group will be compared with the placebo group. If the result shows a statistical significance, go to Step 2.

- Step 2: The 40 mg group will be compared with the placebo group.

(b) Secondary analysis

Each of the MT-5199 groups (40 mg group and 80 mg group) will be compared with the placebo group by means of an analysis using an analysis-of-covariance (ANCOVA) model with group and underlying disease as fixed effects and baseline as a covariate. Missing values will not be imputed.

The same analysis as "(a) Primary analysis" will be performed using the PP analysis set. However, no adjustment for multiplicity will be made.

- Percentage of subjects with a 50% or greater improvement from baseline in the AIMS total score (Items 1 to 7; central assessment [redacted]) at Week 6

- Change from baseline in the AIMS total score (Items 1 to 12; assessment by the investigator [or subinvestigator]) at Week 6

- CGI-TD score at Week 6

The percentage of subjects with a 50% or greater improvement from baseline in the AIMS total score (Items 1 to 7; central assessment [redacted]) at Week 6 will be compared between each of the MT-5199 groups (40 mg group and 80 mg group) and the placebo group by means of the Cochran-Mantel-Haenszel test (CMH test) with underlying disease as a stratification factor.

The change from baseline in the AIMS total score (Items 1 to 12; assessed by the investigator [or subinvestigator]) at Week 6 will be analyzed in the same manner as in "(a) Primary analysis" in "1) Primary efficacy endpoint." However, no adjustment for multiplicity will be made.

The CGI-TD score at Week 6 will also be analyzed in the same manner as in "(a) Primary analysis" in "1) Primary efficacy endpoint." However, no covariates will be included in the model and no adjustment for multiplicity will be made.

2) Exploratory endpoint

- Changes in the EQ-5D-5L score at each assessment point

No special statistical analysis will be performed.

(2) Extension period

For each endpoint, descriptive statistics of the measurement value and the change from baseline will be calculated for each evaluation time point during the period from Week 8 until Week 48. For the AIMS total score (Items 1 to 7; central assessment [redacted]), descriptive statistics of the change from Week 6 will also be calculated for subjects who were randomized to the placebo group in the double-blind period and then re-randomized in the extension period.

13.3.2 Safety Endpoints

Analyses will be performed using the safety analysis set.

The number of subjects with and the incidence of adverse events and adverse drug reactions will be tabulated. For laboratory test values (except for urinalysis), vital signs, 12-lead ECG, SAS, BARS, MMSE-J, JCDSS, PANSS, MADRS-J, and YMRS, descriptive statistics of the measurement value and the change from baseline will be calculated for each evaluation time point. For laboratory test values (urinalysis), a shift table for changes from baseline will be presented for each evaluation time point. For C-SSRS, the number and percentage of subjects will be tabulated.

13.3.3 Pharmacokinetics Endpoints

Descriptive statistics (number of subjects, mean, standard deviation, minimum, median, and maximum) of the plasma concentrations of unchanged drug (MT-5199) and metabolites (NBI-98782 and NBI-136110) at each blood sampling time point will be calculated by treatment group for each scheduled blood sampling point.

Detailed methods of pharmacokinetic analysis will be described in the statistical analysis plan.

13.3.4 Significance Level and Confidence Intervals

Statistical tests will be 2-sided tests performed at the 5% level of significance. Two-sided confidence intervals (CIs) will be used with a confidence coefficient of 95%.

13.4 Modifications in the Statistical Analysis Plan

If any changes are made to the statistical analysis plan specified in this section before data lock, the reason for such changes will be provided in the statistical analysis plan and the clinical study report. If any changes are made to the analytical methods or any additional analyses are performed after data lock, the reason for such changes will be provided in the statistical analysis plan and the clinical study report, and results of these analyses will be

differentiated from those of the planned analyses.

14 PROTOCOL COMPLIANCE, DEVIATIONS AND CHANGES

14.1 Protocol Agreement and Compliance

The investigator must fully examine the appropriateness of the conduct of the study from an ethical and scientific standpoint in consultation with the sponsor, based on the protocol, the latest investigator's brochure, and other necessary documents provided by the sponsor, before reaching an agreement with the sponsor on the protocol.

Based on the results of consultation, the investigator will agree on the contents of the protocol with the sponsor, and will sign or seal and date the agreement, along with the sponsor, to witness they have agreed to comply with the protocol.

14.2 Protocol Deviations or Changes

The investigator (or subinvestigator) must not deviate from or change the protocol without prior written agreement between the investigator and the sponsor as well as written approval of the IRB based on prior reviews. However, the investigator (or subinvestigator) may deviate from or change the protocol due to any unavoidable medical reason such as for elimination of immediate hazards of the subject without either prior written agreement of the sponsor or prior approval of the IRB.

In such cases, the investigator is obliged to provide the sponsor, head of the study site, and IRB for their approval with the contents of and reasons for the deviation or change, and where it is needed to amend the protocol, with a draft amendment as soon as possible and to subsequently obtain the written agreement of the head of the study site and the sponsor.

The investigator (or subinvestigator) must record all actions related to protocol deviations. The investigator will be required to prepare a document describing the reasons for protocol deviations associated with medically unavoidable circumstances, such as deviations to avoid subject's emergency danger, to promptly submit the document to the sponsor and the head of the study site, and to retain a copy of the document.

The investigator will promptly submit, to the sponsor, the head of the study site, and the IRB, a report of any study-related changes that may significantly affect the conduct of the study or increase risks to subjects.

15 PROTOCOL AMENDMENT

If any amendment to the protocol is judged necessary during the course of the study, the sponsor will amend the protocol. After obtaining agreement on the contents of the amendment in consultation with the investigator, the sponsor will immediately notify the head of the study site of the amendment in writing and obtain approval of the IRB through the head of the study site.

If the sponsor is instructed on protocol amendment by the head of the study site based on the opinion of the IRB, the sponsor will judge whether the amendment is appropriate and amend the protocol if necessary. After obtaining agreement on the contents of the amendment in consultation with the investigator, the sponsor will immediately notify the head of the study site of the amendment in writing and obtain approval of the IRB through the head of the study site.

If it is determined necessary to amend the protocol as a result of discussion with the investigator, the sponsor will judge whether the amendment is appropriate and amend the protocol if necessary. After obtaining agreement of the investigator on the contents of the amendment, the sponsor will immediately notify the head of the study site of the amendment in writing and obtain approval of the IRB through the head of the study site.

16 TERMINATION OR SUSPENSION OF THE STUDY

16.1 Criteria for Termination or Suspension of the Study

In the following circumstances, the sponsor will decide on the appropriateness of continuing the study at all or some of the study sites.

(1) The sponsor obtains information related to the quality, efficacy, or safety of the study drug, or other important information related to the proper conduct of the study,

(2) Any amendment to the protocol becomes necessary, and the study site becomes adopt the relevant amendment,

(3) The head of the study site instructs the sponsor to make corrections to the protocol etc. based on the opinions of the IRB, and the sponsor cannot accept the relevant corrections,

(4) The head of the study site instructs the sponsor to discontinue the study based on the decision of the IRB, or

(5) The study site commits significant or persistent violation of the GCP, the protocol, or the study contract.

16.2 Termination or Suspension of the Entire Study Based on the Decision of the Sponsor

If the sponsor decides on termination or suspension of the entire study, it will promptly notify the head of the study site as well as regulatory authorities of the decision on and reason for such termination or suspension in writing. Immediately after being notified of the decision on termination or suspension of the study by the sponsor, the head of the study site will notify the investigator and the IRB of the decision on and detailed reason for termination or suspension of the study in writing.

Immediately after being notified of the decision on termination or suspension of the study by the sponsor through the head of the study site, the investigator will notify subjects accordingly and assure subsequent treatment for the subjects.

Refer to Section 12.3 "Procedures for Withdrawal of Subjects" for actions taken for subjects in the event of study discontinuation.

16.3 Termination or Suspension of the Study at the Relevant Study Site Based on the Decision of the Investigator or the IRB

If the investigator decides on termination or suspension of the study at his/her own discretion, the investigator will immediately notify the head of the study site of the decision on and

detailed reason for such termination or suspension in writing. The head of the study site will immediately notify the sponsor and the IRB thereof in writing.

If the IRB decides on termination or suspension of the study at its own discretion, the IRB will immediately notify the head of the study site of the decision on and detailed reason for termination or suspension in writing. The head of the study site will immediately notify the investigator and the sponsor thereof in writing.

16.4 Termination of the Study Based on Cancellation of the Contract with the Study Site

If the sponsor terminates the study due to significant or persistent violation of the GCP, the protocol, or the study contract by the study site during the study period, the sponsor will immediately report the matter to the regulatory authorities.

17 MATTERS RELATED TO THE CASE REPORT FORM

17.1 Format of the Case Report Form

[redacted]

17.2 Identification of Data Entered Directly in the Case Report Form and Handled as Source Documents

For the items listed below, data recorded in the case report form will be handled as source documents. If medical records, etc., contain applicable data, however, these data will be handled as source documents.

[redacted]

If entries other than the above are handled as source documents, they should be specified and documented separately by the sponsor and the investigator before the start of the study.

17.3 Precautions for Entry in the Case Report Form

The investigator (or subinvestigator) or a clinical study collaborator will prepare the case report form according to the following specifications. The case report form will be prepared according to the Procedures for "Changes/Corrections to Case Report Forms" separately provided by the sponsor.

(1) Prior to entry in the case report form, the sponsor will issue user ID and password to the investigator (or subinvestigator) and a clinical study collaborator for user management. The user ID and password issued should be managed individually and should not be shared by the investigator (or subinvestigator) and a clinical study collaborator. Data entry should be made by the investigator (or subinvestigator) and a clinical study collaborator who are authorized for data entry.

(2) Case report forms will be prepared for subjects for whom the initial randomization of the study drug has been completed.

(3) The investigator is authorized to make all entries in the case report form. The subinvestigator is authorized to make all entries in the case report form except for electronic signature. The clinical study collaborator is authorized to transcribe contents from source documents requiring no medical judgment, such as medical records.

(4) In the case of making changes or corrections to the entries in the case report form, the reason for the change or correction should be recorded as electronic information.

(5) After confirming that the case report form has been created accurately and completely and that the audit trail and the information on electronic signature can be accessed, the investigator will affix his/her electronic signature to the case report form on the EDC system.

(6) The investigator will retain copies of case report forms preserved in CD-R or other recording media (containing the electronic case report form that has been confirmed by the investigator for its content, stored as PDF files). During the period after electronic signature to the provision of the copies on CD-R or other recording media by the sponsor, an environment where the electronic case report forms are accessible (with the access authorization to the EDC system) will be provided as an alternative to substitute the absence of the copies.

(7) If any inconsistency is found between the data recorded in the case report form and the source document, the investigator will prepare a record explaining the reason, submit it to the sponsor, and retain a copy of the record.

17.4 Timing of Case Report Form Submission

After performing the specified tests and observations, the investigator (or subinvestigator) will promptly [redacted] enter the results in the electronic case report form.

18 DIRECT ACCESS TO SOURCE DOCUMENTS ETC.

The investigator and head of the study site will accept monitoring and auditing by the sponsor as well as inspections by the IRB and regulatory authorities and assure that all study-related documents are supplied for direct access.

19 QUALITY CONTROL AND QUALITY ASSURANCE OF THE STUDY

In order to maintain quality and reliability of the study, the sponsor must implement "quality control of the study" and "quality assurance of the study" based on the Mitsubishi Tanabe Pharma Corporation GCP SOPs. The study site and investigator must cooperate in quality control and quality assurance of the study implemented by the sponsor.

For quality control of the study, the monitor will visit the study site for direct access at appropriate intervals to confirm that the study is conducted in compliance with study-related operating procedures of the relevant study site, the latest protocol and GCP. The monitor will also confirm that the entries in the case report form reported by the investigator (or subinvestigator) are accurate and complete, and are verifiable against study-related records such as source documents.

To assure that the study is conducted in compliance with the protocol and GCP, the auditor will confirm, by auditing according to the GCP SOPs, that quality control of the study is implemented appropriately.

20 ETHICS

20.1 Ethical Conduct of the Study

This clinical study must be conducted in compliance with the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices, GCP, and the protocol, while paying attention to the ethical principles based on the Declaration of Helsinki.

20.2 Institutional Review Board

The IRB will evaluate the appropriateness of the conduct and continuation of the study from ethical, scientific, and medical/pharmaceutical perspectives, according to the contents of the investigator's brochure, protocol, and informed consent documents.

20.3 Subjects' Confidentiality

Subjects will be identified by subject ID codes in the registration form and case report form. All persons involved in the study will keep information identifying subjects confidential during the course of direct access to study-related source documents, publication of study results in medical journals, submission of study-related data to regulatory authorities, etc.

21 RETENTION OF RECORDS ETC.

21.1 Records etc. to Be Retained at the Study Site

The person responsible for record retention designated by the head of the study site will retain study-related documents and records to be retained in the study site until one of the following (1) or (2) whichever is latest. If the sponsor requires retention for a longer period, the study site will consult with the sponsor regarding the period and method of retention.

If the sponsor decides not to attach materials on study results to the approval application form, the sponsor will report the decision and the reason for it to the head of the study site in writing.

If the sponsor obtains the marketing approval of the investigational product or fails to obtain the marketing approval and therefore decides to discontinue the development of the investigational product, the sponsor will report the decision to the head of the study site in writing.

(1) The date of marketing approval pertaining to the investigational product (in case a notification about the discontinuation of development or to the effect that the study results will not be attached to the approval application form was received, the date after 3 years from receipt of the notification)

(2) The date after 3 years from study discontinuation or completion.

21.2 Records to Be Retained by the Sponsor

The sponsor will retain study-related documents and records to be retained by the sponsor until one of the following (1) or (2) whichever is latest.

(1) The date after 5 years from the date of marketing approval pertaining to the investigational product (in case the development was discontinued, the date after 3 years from the decision that development would be discontinued), or the date of completion of reexamination

(2) The date after 3 years from study discontinuation or completion.

22 PAYMENT

Cash payment to subjects and the study site will be decided based on the contract or agreement between the study site and the sponsor.

23 COMPENSATION FOR INJURY AND INSURANCE

23.1 Compensation for Injury

In the event that the conduct of this study causes injury to a subject, the sponsor will provide appropriate compensation in accordance with its own standards, except in cases where the causal relationship to the study is ruled out (compensation consists of medical expenses [self-paid amount], medical allowance, and compensation money). In this case, the subject will not be burdened with the process of demonstrating a causal relationship, etc.

23.2 Insurance

The sponsor will take appropriate action, such as applying for insurance, to assume responsibility for study-related health injury compensation or liability.

24 ARRANGEMENTS FOR PUBLICATION

Information in this protocol belongs to the sponsor, and will be provided to persons involved in the study including the investigator (or subinvestigator) and the IRB. This information may not be disclosed to any third party without prior written consent of the sponsor except as needed to conduct the study properly.

If persons involved in the study at the study site including the investigator (or subinvestigator) publish information obtained from this study in academic conferences, etc., prior approval of the sponsor must be obtained.

The sponsor is free to use the information obtained from this study for purposes such as reporting to regulatory authorities, proper use of drugs, marketing, etc.

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Contact numbers during non-business hours and for emergency

During nighttime (5:30 p.m. to 9:00 a.m. on the next day) and on Saturdays, Sundays, national holidays, and other holidays such as the end of the year and the beginning of the year, the Emergency Contact Center shown below will relay emergency calls to the clinical research associate.

Mitsubishi Tanabe Pharma Corporation Emergency Contact Center

TEL: [redacted]

Address
[redacted]