Statistical Analysis Plan

Protocol No. MT-5199-J02

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

(A Confirmatory Trial and the Long Term Exposure Trial)

Study Sponsor	Mitsubishi Tanabe Pharma Corporation
Version No.	1
Date	November 12, 2020

APPROVAL FORM

Statistical Analysis Plan

Protocol No.	MT-5199-J02
Protocol 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 (A Confirmatory Trial and the Long Term Exposure Trial)
Protocol Version	ver. 3.0
(Date)	(August 6, 2019)

Authors:

Statistics Author

Print Name: [redacted]

Position: COT STAT

Clinical Pharmacokinetics Author

Print Name: [redacted]

Position: COT CP

Approved by:

Statistic Approver

Print Name: [redacted]

Position: Responsible STAT

Signature: Refer to the mail

Approval Date: Refer to the mail

Clinical Pharmacokinetic Approver

Print Name: [redacted]

Position: Responsible CP

Signature: Refer to the mail

Approval Date: Refer to the mail

CONTENT

CONTENT iiii
List of Abbreviations vii
Definition of Terms viii
1. Introduction 1
2. Study Objectives and Endpoints 1
2.1. Study Objectives 1
2.2. Investigation Items 1
2.2.1. Primary Endpoint 1
2.2.2. Secondary Endpoints 1
2.2.3. Exploratory Endpoints 1
2.2.4. Safety Endpoints 1
2.2.5. Pharmacokinetic Endpoints 2
2.2.6. Pharmacodynamic Endpoints 2
3. Study Design 2
3.1. Study Design 2
3.2. Evaluation period 3
3.2.1. Efficacy and Safety Measurements Assessed and Flow Chart 4
3.3. Determination of Sample Size 8
4. Planned Analysis 8
4.1. Intermediate Analysis 8
4.2. Final Analysis 9
4.3. Data Monitoring Committee 9
5. Analysis Sets 9
5.1. Efficacy Analysis Set 9
5.2. Safety Analysis Set 9
5.3. Pharmacokinetic Analysis Set 9
6. Statistical Issues 9
6.1. Statistical Descriptive Statistics 9
6.2. Statistical Test 10
6.2.1. Significance Level and Confidence Coefficient 10
6.2.2. Issues on Statistical Analysis 10
7. Data Handling 10
7.1. Definition of Derived Variables 10

7.1.1. Age at the Time of Obtaining Informed Consent 10
7.1.2. BMI 11
7.1.3. Days of Treatment and Study Drug Administration 11
7.1.4. Dosing Proportion 11
7.1.5. Visit for Dose Reduction 12
7.1.6. Chlorpromazine Conversion Factor 12
7.1.7. Anticholinergic Drug 12
7.1.8. Hepatic Function Abnormality 12
7.1.9. Age of Onset 12
7.1.10. Disease Duration 12
7.1.11. QT Interval Correction Value 12
7.1.12. Score and Refence Visit 12
7.2. Definition of Visit Windows 16
7.2.1. Visit Windows 16
7.2.2. Allowance of Deviation at the Visit 17
7.3. Handling of Data for Missing Values 17
7.4. Handling of Data for AIMS Evaluation Results 17
7.5. Handling of Values of the Quantification Limit or Less of Clinical Laboratory Test 17
7.5.1. Case for the Continuous Values Is Reported as Less than the Quantification Limit 17
7.5.2. Case for the Continuous Values Is Reported as the Quantification Limit or Less or the Quantification Upper Limit or More 18
7.6. Handling of Data Related to Evaluation of Pharmacokinetics 18
8. Statistical Methods 18
8.1. Subjects Registered in the Trial 18
8.1.1. Subjects Discontinued in the Trial 18
8.1.2. Breakdown of Subjects 19
8.1.3. Demographic and the Other Baseline Characteristics 19
8.1.4. Medical History 20
8.1.5. Status of Pretreatment or Concomitant Medications 20
8.1.6. Status in Treatment and Administration of Study Drug 20
8.2. Efficacy Analysis 21
8.2.1. Main Analysis 21
8.2.2. Stratified Efficacy Analysis 22
8.2.3. Other Efficacy Analysis 23
8.3. Safety Analysis 25

8.3.1. Adverse Events 25
8.3.2. Laboratory Test 27
8.3.3. Vital Signs 27
8.3.4. 12-lead ECG 28
8.3.5. Psychiatric Symptomatology Assessment Scales 28
8.4. Pharmacokinetic Analysis 28
8.5. Pharmacodynamic Analysis 29
9. Numerical Description 29
9.1. Number of Displayed Digits 29
10. Changes in the Analysis Plan from the Protocol 29
11. Software Used 29
12. References 29
13. Appendix 30
13.1. Antipsychotic Drugs 30
13.2. EQ-5D-5L Score Conversion Table (Japanese) 31
13.3. The Types of Adverse Events of Special Interest (AESI) 32

List of Abbreviations

Abbreviation	Expanded term
AIMS	Abnormal Involuntary Movement Scale
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AUC	Area under the plasma concentration-time curve
BARS	Barnes Akathisia Rating Scale
BL	Baseline
BMI	Body mass index
CDSS	Calgary Depression Scale for Schizophrenics
CFB	Change from Baseline
CGI-TD	Clinical Global Impression of Change – Tardive Dyskinesia
C_{max}	Maximum plasma concentration
CMH	Cochran-Mantel-Haenszel
CP	Chlorpromazine
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	Cytochrome P450
DBP	Diastolic Blood Pressure
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
EDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EQ-5D-5L	Euro QoL 5-dimension 5-level
GCP	Good Clinical Practice
HBs	Hepatitis B surface
HCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HDL	High density lipoprotein
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ITT	Intent-to-Treat
LS Mean	Least squares Mean
MADRS	Montgomery-Åsberg Depression Rating Scale

Abbreviation	Expanded term
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
PCSC	Potentially Clinically Significant Criteria
PP	Per-Protocol
PT	Preferred term
QOL	Quality of life
QTcF	Fridericia's correction of QT interval
SAE	Serious adverse event
SAS	Simpson-Angus extrapyramidal side effects scale
SBP	Systolic Blood Pressure
SD	Standard Deviation
SE	Standard Error
$t_{1/2}$	Terminal elimination half-life
TD	Tardive Dyskinesia
ULN	Upper limit of normal
VMAT2	Vesicular monoamine transporter 2
WHO	World Health Organization
YMRS	Young Mania Rating Scale

Definition 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).
Adverse event	Clinically unfavorable or unintended signs (including clinically significant abnormal laboratory test values), symptoms, or disease observed from the start of study drug administration to 4 weeks after the follow-up period or 4 weeks after discontinuation of study drug administration. It may or may not have a causal relationship with the study drug.
AIMS responder	Subjects who have a ≥50% improvement from baseline in the AIMS total score.

1. Introduction

This plan is a document that shows more detailed contents of the statistical analysis plan for the efficacy and safety of MT-5199 in addition to the statistical analysis plan described in the clinical trial protocol, which is "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 (A Confirmatory Trial and The Long Term Exposure Trial) [Clinical trial protocol number: MT-5199-J02]."

2. Study Objectives and Endpoints

2.1. Study Objectives

To evaluate the efficacy and safety of repeated oral doses of MT-5199 (40 mg or 80 mg) in patients with schizophrenia, schizoaffective disorder, bipolar disorder, or depressive disorder who have tardive dyskinesia (TD)

- To examine the superiority of MT-5199 (40 mg and 80 mg) over placebo using the change from baseline in the AIMS total score (items 1 to 7, central assessment [redacted]) at Week 6 of study treatment as an index
- To evaluate the safety of MT-5199 (40 mg/day or 80 mg/day) administered for 6 weeks and the efficacy and safety in a long-term extension period for 42 weeks

2.2. Investigation Items

2.2.1. Primary Endpoint

The primary endpoint of this study is the change from baseline in the AIMS total score (items 1to 7, central assessment [redacted]) at Week 6.

2.2.2. Secondary Endpoints

- Percentage of subjects with a ≥50% improvement from baseline in the AIMS total score (items 1 to 7, central assessment [redacted]) at Week 6 of study treatment
- Change from baseline in the AIMS total score (site rater* by investigator [or sub-investigator]) at Week 6 of study treatment
  *Total score of items 1 to 7 out of items 1 to 12 evaluated by the investigator (or sub-investigator)
- CGI-TD score at Week 6 of study treatment

2.2.3. Exploratory Endpoints

- Change in EQ-5D-5L score at each visit

2.2.4. Safety Endpoints

- All Subjects
  (1) adverse events and adverse reactions
  (2) laboratory tests
  (3) vital signs
  (4) physical findings
  (5) 12-lead ECG

(6) C-SSRS: Assessment of suicidal ideation and suicide attempts
(7) SAS: Assessment of extrapyramidal symptoms
(8) BARS: Assessment of drug-induced akathisia
(9) MMSE-J: Assessment of cognitive function

- Subjects with schizophrenia or schizoaffective disorder
  (10) JCDSS: Assessment of depressive symptoms
  (11) PANSS: Assessment of the underlying disease

- Subjects with bipolar disorder or depressive disorder
  (12) MADRS-J: Assessment of depressive symptoms
  (13) YMRS: Assessment of manic symptoms

2.2.5. Pharmacokinetic Endpoints

- Plasma concentrations of unchanged drug (MT-5199) and metabolite (NBI-98782 and NBI-136110) concentrations

2.2.6. Pharmacodynamic Endpoints

- Not applicable.

3. Study Design

3.1. Study Design

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

Overview of the study design is shown in Figure 1.

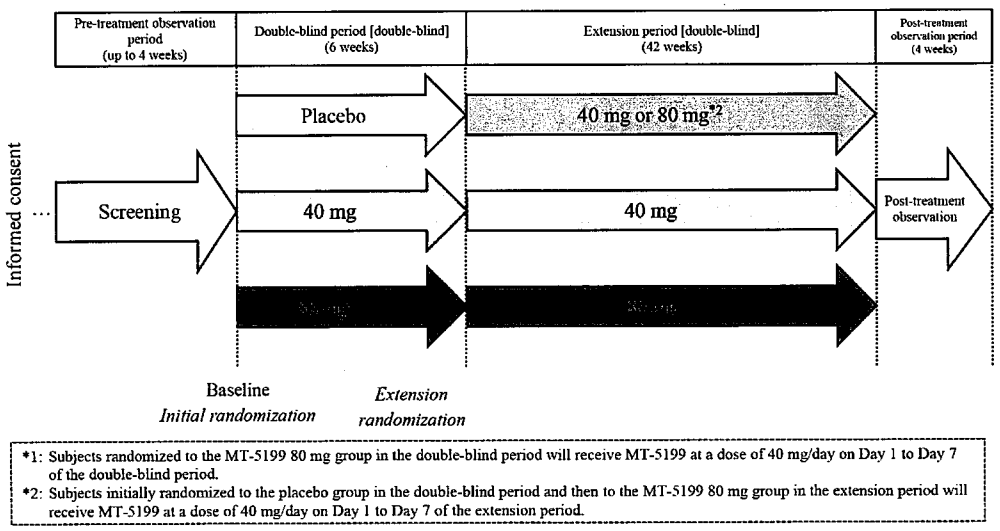

Figure 1 Overview of the Study Design

3.2. Evaluation period

The examination and observation schedule for this study is shown in 3.2.1 Examination and Observation Schedule.

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

The pre-treatment observation period is up to 4 weeks between the day of the screening test/observation (except for some investigations related to subject demographics in 3.2.1.3 Examination / Observation Items) and initial randomization.

(2) Double-blind period (6 weeks)

The double-blind period is 6 weeks from the following day of initial randomization. The prescribed consultation date is calculated from the start date of the double-blind period as the first day of administration, and Weeks 2, 4, and 6 of treatment. And placebo, MT-5199 40 mg, or MT-5199 80 mg is 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. The prescribed consultation date shall be Weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 of treatment, counting the start date of the double-blind period as the first day of administration. And MT-5199 40 mg or 80 mg is 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 day after the completion (or discontinuation) of the study treatment. The prescribed consultation date is 4 weeks after the end (discontinuation) of administration.

(5) Long-term exposure (48 weeks)

The long-term exposure is from the double-blind period to the extension period, and is intended for subjects excluding subjects who are discontinued from the double-blind period after being assigned to the placebo group.

(6) Placebo-controlled short-term treatment (6 weeks)

The placebo-controlled short-term is used as an antonym for long-term exposure.

3.2.1. Examination and Observation Schedule

3.2.1.1. 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 (days)				± 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 ECG		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 treatment				<═══	═══	═══>	<═══	═══	═══	═══	═══	═══	═══	═══	═══	═══	═══>	
Study treatment 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 is to be measured at screening, and only body weight is to be measured at other visits. *4: Only for women of childbearing potential.

*5: HbA1c is to 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 are to be investigated for the period from 90 days before the start of the pre-treatment observation period, and drugs used for other purposes are to be investigated for the period at and 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).

3.2.1.2. 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 [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 (days)				± 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 ECG		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 treatment				<═══	═══	═══>	<═══	═══	═══	═══	═══	═══	═══	═══	═══	═══	═══>	
Study treatment 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 at and 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).

3.2.1.3. Examination / Observation Items

Examination/ Observation Items		Contents
Subject Demographics		Gender, date of birth, height, weight (at enrollment), race, ethnicity, underlying disease, diagnosis time of underlying disease, diagnosis time of TD, complications
Vital Signs		Temperature (axillary), body weight, systolic blood pressure, diastolic blood pressure, pulse rate
12-lead ECG		QT, QRS, PR interval, RR interval, heart rate, findings
Laboratory Tests	Hematology	White blood cell count, white blood cell fraction (neutrophil, lymphocyte, monocyte, eosinophil, basophil), red blood cell count, hemoglobin, hematocrit, platelet count
	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, prolactin (blind item)
	Urinalysis (qualitative)	Glucose, protein, occult blood (reference range: -, ±, 1+, 2+, 3+, 4+, 5+)
Other Examinations		CYP2D6 genotyping (blind item), infectious disease / virus test, pregnancy test (only for women of childbearing potential)

Refer to 13. Appendix for AIMS, CGI-TD, EQ-5D-5L and various psychological symptomatology evaluation scales.

3.3. Determination of Sample Size

240 subjects (double-blind period: 80 subjects per group)

[redacted]

4. Planned Analysis

4.1. Intermediate Analysis

Not planned for this trial.

4.2. Final Analysis

Refer to chapter 8. Statistical Methods.

4.3. Data Monitoring Committee

Not installed in this trial.

5. Analysis Sets

5.1. Efficacy Analysis Set

(1) Intent-to-Treat (ITT) analysis set (main analysis population)
The ITT analysis set consisted 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 [redacted]) is available, and
- Subjects for whom ≥1 AIMS total score (items 1 to 7: central [redacted]) after baseline is available in the double-blind period

(2) Per-Protocol (PP) analysis set
The PP analysis set consisted 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 [redacted]) at Week 6 of study treatment is available,
- Subjects without significant protocol deviations related to efficacy, and
- Subjects who are 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 of study treatment is detectable

5.2. Safety Analysis Set

The safety analysis set consisted of subjects who satisfy both of the following conditions:
- Subjects who are randomized and took the investigational product, and
- Subjects for whom postbaseline safety data are available

5.3. 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 investigational product at all
- Subjects with no drug concentration data after investigational product administration.

6. Statistical Issues

6.1. Statistical Descriptive Statistics

The following descriptive statistics are calculated for each item with continuous values, unless otherwise specified.
Number of subjects, mean, standard deviation, minimum, median, maximum

6.2. Statistical Test

6.2.1. Significance Level and Confidence Coefficient

Statistical tests are 2-sided tests performed at a 5% level of significance. Two-sided confidence intervals are used with a confidence coefficient of 95%.

6.2.2. Issues on Statistical Analysis

6.2.2.1. Adjustment by covariates

In the primary analysis of the primary efficacy endpoint, the adjustment is made using the baseline value of the AIMS total score (items 1 to 7: central [redacted]) as a covariate as mentioned in 8.2 Efficacy Analysis.

6.2.2.2. Handling of subject dropouts or missing measurements

The handling for subject dropouts or missing measurements of endpoints related to efficacy are described in 7.3 Handling of Data for Missing Values and are omitted here.

6.2.2.3. Intermediate Analysis and Data Monitoring

Not planned.

6.2.2.4. Multicenter study

In this study, the number of cases in each dose group per site is small, and it is considered that the site effect cannot be examined. Therefore, the site effect is not examined.

6.2.2.5. Multiple comparison/multiplicity

In this study, in the primary analysis for the primary efficacy endpoint, the multiplicity in the multigroup comparison is adjusted by fixed-sequence procedure for comparison between treatment groups. In addition, for the secondary analysis of the primary endpoint and the analysis of the secondary endpoints the multiplicity between evaluation endpoints and visits are not adjusted.

6.2.2.6. Comparison of subjects using the effectiveness assessment subgroups

For the primary endpoint and the AIMS responder (subjects whose AIMS total score [Items 1 to 7: central [redacted]] improved by 50% or more from the baseline) the same analysis in the PP subgroup is performed as well.

6.2.2.7. Trials with active controls intended to confirm equivalence

Not applicable.

7. Data Handling

After the examination and observation of all subjects are completed, the handling of subjects is decided according to "5 Analysis Sets." If it is necessary to consider the handling of subjects for matters not specified in "5 Analysis Sets," handling rules of the subjects and handling of subjects should be determined according to the procedure specified in the sponsor's GCP standard operating procedure manual.

The handling of subjects and the handling of data are as follows. The handling of data other than the following was decided at the case review meeting [redacted].

7.1. Definition of Derived Variables

7.1.1. Age at the Time of Obtaining Informed Consent

Age (years) = date of obtaining informed consent (year value) − date of birth (year value)

However when "date of obtaining informed consent (month value) < date of birth (month value)" or "date of obtaining informed consent (month value) = date of birth (month value) and date of obtaining informed consent (day value) < date of birth (day value)," subtract 1 from the age calculated above.

7.1.2. BMI

BMI (kg/m^2) = body weight (kg) / {height (m)}^{2}
Rounded to one decimal place and displayed with one decimal place.

7.1.3. Days of Treatment and Study Drug Administration

The treatment period is the period of the study drug administration in the double-blind period and the extension period. The number of days that the subject actually takes the study drug during the treatment period is defined as days of study drug administration.

7.1.3.1. Days of treatment

- Double-blind period
  Case of complete cases: days of treatment = date of Week 6 - the first randomization date
  Case of discontinued cases: days of treatment = discontinuation date - the first randomization date
  * If the first randomization date = treatment start date (corresponds to deviation from the clinical trial protocol), add 1 day to the above number of days in both cases.
- Extension period
  Case of complete cases: days of treatment = date of Week 48 - date of Week 6
  Case of discontinued cases: days of treatment = discontinuation date - date of Week 6

For days of treatment in long-term exposure, the total days both in the double-blind period and the extension period are used.

7.1.3.2. Days of study drug administration

The number of days of drug administration is calculated at the following evaluation periods and at the visits. If the number of days of drug administration is less than 0, it is set to 0.

- Days of study drug administration for each evaluation period
  Days of study drug administration = days of treatment - total number of days without drug administration reported during the relevant evaluation period
- Days of study drug administration for each visit
  Days of study drug administration = (date of visit or discontinuation date - treatment start date or date of previous visit, whichever occurs later or the latest date of previous visit) - number of days without drug administration reported at the visit

For days of study drug administration in long-term exposure, the total days both in the double-blind period and the extension period are used.

7.1.4. Dosing Proportion

7.1.4.1. Dosing Proportion for Each Evaluation Period

Calculate according to 7.1.3. Days of treatment and study drug administration for each evaluation period.

- Double-blind period
  Dosing proportion (%) = days of study drug administration / days of treatment × 100
- Extension period
  Dosing proportion (%) = days of study drug administration / days of treatment × 100

For days of study drug administration and days of treatment in long-term exposure, the total days both in the double-blind period and the extension period are used.

7.1.4.2. Dosing Proportion for Each Visit

Calculate according to 7.1.3. Days of treatment and days of study drug administration for each visit.

➢ Dosing proportion (%) = days of study drug administration / (date of visit at each visit window or date of discontinuation of administration - date of the first randomization or date of previous visit, whichever occurs later) × 100

7.1.5. Visit for Dose Reduction

The visit of dose reduction in the extension period is defined as follows:

- Case of the dose reduced on the day of visit: a visit point corresponding to the day of visit
- Case of the dose reduced on the day other than visit: a visit point corresponding to the day of visit immediately after.

Example) If dose is reduced on the day of Week 8 of study treatment, the time of dose reduction shall be Week 6 to Week 8 of study treatment. If dose reduced on the day following the day of Week 8 of study treatment, the time of dose reduction shall be Week 8 to Week 12 of study treatment.

7.1.6. Chlorpromazine Conversion Factor

100 mg Chlorpromazine equivalent amounts are shown in the attached table (Appendix 13.1).

7.1.7. Anticholinergic Drug

Anticholinergic drugs are classified as follows.

N04A Anticholinergic agents	N04AA Tertiary amines	N04AA01	Trihexyphenidyl
		N04AA02	Biperiden

7.1.8. Hepatic Function Abnormality

Hepatic function abnormality is defined as when the baseline value of γ-GTP, ALT, or AST exceeds the upper limit of the reference value range.

Reference value:

- γ-GTP: 80 U/L or less for male, 30 U/L or less for female
- ALT: 5–45 U/L
- AST: 10–40 U/L

7.1.9. Age of Onset

7.1.9.1. Age of Onset of Tardive Dyskinesia (TD)

Age of onset of TD (years) = date of obtaining informed consent (year value) - diagnosis time of TD onset (year value)

7.1.9.2. Age of Onset of Underlying Disease

Age of onset of underlying disease (years) = date of obtaining informed consent (year value) - diagnosis time of underlying disease onset (year value)

7.1.10. Disease Duration

7.1.10.1. Duration of Tardive Dyskinesia (TD)

Duration of TD (years) = date of obtaining informed consent (year value) - diagnosis time of TD onset (year value)

7.1.11. QT Interval Correction Value

7.1.11.1. Calculation of QTcF

The following Fridericia's correction formula is used:

$QTcF = QT/3\sqrt{RR}$

7.1.12. Score and Refence Visit

7.1.12.1. Reference Visit for Change From Baseline

The efficacy endpoints and C-SSRS for calculating the change from the reference visit are shown below.

(1) Efficacy endpoints for calculating the change from the reference visit

It corresponds to AIMS and EQ-5D-5L Index Value (VAS).

- Double-blind period
  Reference visit A: Baseline, evaluation period: Weeks 2, 4, and 6 of study treatment
- Extension period and post-treatment observation period: Two reference visits are defined.
  Reference visit A: Baseline, evaluation period: Weeks 16, 32, and 48 of study treatment, Follow up Week 4
  Reference visit B: Week 6, evaluation period: Weeks 16, 32, and 48 of study treatment, Follow up Week 4 after the end of administration

(2) C-SSRS
Reference visit A: Baseline (Past 3 month), evaluation period: Weeks 6, and 48 of study treatment
Reference visit C: Week 48, evaluation period: Follow up Week 4 after the end of administration

7.1.12.2. Score in the Efficacy Evaluation

(1) AIMS total score
Regarding the central [redacted] rater and the evaluation by the investigator (or sub-investigator) on site, regardless of the evaluator, the severity by each of 7 body parts of Muscles of Facial Expression, Lips / Perioral Area, Jaw, Tongue, Upper limbs, Lower limbs, and Trunk is evaluated on a 5-point scale from 0 (none) to 4 (advanced). The total of the evaluation scores of each item (items 1 to 7) is defined as the AIMS total score. In addition, the total score is calculated when all 7 items of data are available.

(2) CGI-TD score
For answer options, read the following scores:
1 = Very Much Improved
2 = Much Improved
3 = Minimally Improved
4 = Not Changed
5 = Minimally Worse
6 = Much Worse
7 = Very Much Worse

(3) EQ-5D-5L Index Value
Use the value (integer value) of Visual Analogue Scale (from 0 to 100) (VAS score). And the scores for each item are defined by replacing the five items of MOBILITY, SELF-CARE, USUAL ACTIVITIES, PAIN/DISCOMFORT, ANXIETY/DEPRESSION with scores as shown below.
From the answers to questions A, B, C, D and E, obtain a 5-digit numerical value in which each item score is arranged side by side, and according to the score conversion table determined by Ikeda et al. Index Value is calculated (1 + estimation of constant term + sum of estimated values of coefficients corresponding to the level of answers except for 1). The part of EQ-5D-5L conversion table in Japan is shown in the Appendix (13.2).

1) Arrange the answer numbers from Mo to Ad side by side to make a 5-digit numerical value (hereinafter referred to as health state). The health state can exist from 11111 to 55555.
2) If all five answers are 1, that is, if the health state is 11111, the index value is 1. If the health state is other than 11111, calculate the index value by the above formula using Constant term: –0.060924 and the estimated value of the coefficient for each level of the answer to each question in the table below. If any one of the five answers is unanswered, the index value of that subject will be treated as a missing.

Item	Level	Estimated Value	Standard Error	p-value
Constants		–0.060924	0.013625	< 0.0001
Mo	2	–0.063865	0.008996	< 0.0001
	3	–0.112618	0.009287	< 0.0001
	4	–0.179043	0.010231	< 0.0001

	5	–0.242916	0.009425	< 0.0001
Sc	2	–0.043632	0.008931	< 0.0001
	3	–0.076660	0.009972	< 0.0001
	4	–0.124265	0.010129	< 0.0001
	5	–0.159659	0.008924	< 0.0001
Ua	2	–0.050407	0.009205	< 0.0001
	3	–0.091131	0.010005	< 0.0001
	4	–0.147929	0.009744	< 0.0001
	5	–0.174786	0.009115	< 0.0001
Pd	2	–0.044545	0.008354	< 0.0001
	3	–0.068187	0.010052	< 0.0001
	4	–0.131436	0.008985	< 0.0001
	5	–0.191203	0.009604	< 0.0001
Ad	2	–0.071779	0.009701	< 0.0001
	3	–0.110496	0.010863	< 0.0001
	4	–0.168171	0.009850	< 0.0001
	5	–0.195961	0.009164	< 0.0001

Mo: MOBILITY, Sc: SELF-CARE, Ua: USUAL ACTIVITIES,
Pd: PAIN/DISCOMFORT, Ad: ANXIETY / DEPRESSION

A. MOBILITY
1= I have no problems in walking about
2= I have slight problems in walking about
3= I have moderate problems in walking about
4= I have severe problems in walking about
5= I am unable to walk about

B. SELF-CARE
1= I have no problems washing or dressing myself
2= I have slight problems washing or dressing myself
3= I have moderate problems washing or dressing myself
4= I have severe problems washing or dressing myself
5= I am unable to wash or dress myself

C. USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*
1= I have no problems doing my usual activities
2= I have slight problems doing my usual activities
3= I have moderate problems doing my usual activities
4= I have severe problems doing my usual activities
5= I am unable to do my usual activities

D. PAIN / DISCOMFORT
1= I have no pain or discomfort
2= I have slight pain or discomfort
3= I have moderate pain or discomfort
4= I have severe pain or discomfort
5= I have extreme pain or discomfort

E. ANXIETY / DEPRESSION
1= I am not anxious or depressed
2= I am slightly anxious or depressed
3= I am moderately anxious or depressed
4= I am severely anxious or depressed
5= I am extremely anxious or depressed

7.1.12.3. Scoring in the Psychiatric Symptomatology Assessment Scales

(1) C-SSRS score
For answer options, read the scores shown below:
0 = No suicidal ideation
1 = Wish to be dead
2 = Non-specific active suicidal thoughts
3 = Active suicidal ideation with any methods (not plan) without intent to act
4 = Active suicidal ideation with some intent to act, without specific plan
5 = Active suicidal ideation with specific plan and intent

(2) SAS global score
Each 10 item of Gait, Arm dropping, Shoulder shaking, Elbow rigidity, Fixation of position or wrist rigidity, Leg pendulousness, Head dropping, Glabella tap, Tremor, and Salivation for evaluating extrapyramidal symptoms is rated on a 5-point scale from 0 (none) to 4 (severe). The total of the evaluation scores (items 1 to 10) is defined as a global score.

(3) BARS total score/global score
Akathisia objective and subjective symptoms and distress of subjective symptoms are rated on a 4-point scale from 0 to 3, respectively. The total of the evaluation scores of items 1 to 3 is taken as the total score. In addition, the comprehensive clinical score of akathisia is rated on a 6-point scale from 0 (none) to 5 (severe), and the score is defined as the global score.

(4) MMSE-J total score
It consists of 11-question measure that tests cognitive function such as orientation, registration, attention and calculation, language function, behavior for verbal commands and graphic copying, etc. The first 5 questions are the verbal exams, and the latter 6 questions are an operability exams. The total of these scores is defined as the total score.

(5) JCDSS total score
A total of 9 items, consisting of 8 items related to subjective symptoms and 1 item related to objective symptoms based on observation, are evaluated on a 4-point scale from 0 (none) to 3 (severe). The total of the evaluation scores (items 1 to 9) is defined as the total score. In this trial, the evaluation is performed only for subjects who have the underlying disease of schizophrenia or schizoaffective disorder.

(6) PANSS total score in Positive scale/Negative scale/General Psychopathology scale and Composite scale score
A total of 30 items, consisting of 7 items on the positive scale, 7 items on the negative scale, and 16 items on the general psychopathology scale, are evaluated on a 7-point scale from 1 (none) to 7 (most severe). The total of the evaluation scores of each item (P1 to P7) on the positive scale is the total score in the positive scale, and the total of the evaluation scores of each item (N1 to N7) on the negative scale is the total score in the negative scale. The total of the evaluation scores of each item (G1 to G16) on the general psychopathology scale is defined as the total score in general psychopathology scale. In this trial, the evaluation is performed only for subjects who have the underlying disease of schizophrenia or schizoaffective disorder. The Composite scale score is defined as the difference of the total score of positive scale minus the total score of negative scale.

(7) MADRS-J total score

The score increment of the anchor point is 2 points, and 10 items related to depressive symptoms are evaluated on a 7-point scale from 0 to 6. The total of the evaluation scores of each item (items 1 to 10) is defined as the total score.

In this trial, the evaluation is performed only for subjects who have the underlying disease of bipolar disorder or depressive disorder.

(8) YMRS total score

A total of 11 items, consisting of Elevated Mood, Increased Motor Activity-Energy, Sexual Interest, Sleep, Irritability, Speech (Rate and Amount), Language-Thought Disorder, Content, Disruptive-Aggressive Behavior, Appearance and Insight are evaluated on a 5-point scale. The points to note are that the scores of the four items of Irritability, Speech, Content, Disruptive-Aggressive Behavior are a five-point scale of 0, 2, 4, 6 and 8, and the scores of the other 7 items are a 5-point scale of 0, 1, 2, 3 and 4. The total of the evaluation scores of each item (items 1 to 11) is defined as the total score (evaluation in the range of 0 to 60). In this trial, the evaluation is performed only for subjects who have the underlying disease of bipolar disorder or depressive disorder.

7.2. Definition of Visit Windows

7.2.1. Visit Windows

Each item is tabulated by evaluation time point (hereinafter as visit) defined in the section 9.1. Schedule of the clinical trial protocol. The reference day and allowable time window (hereinafter as visit windows) for each visit are shown below. When the administration of the study drug is discontinued, it is not aggregated as the visit, but if the data at the time of discontinuation of the study drug administration falls within the visit window, it is used as the data at the corresponding visit.

Evaluation other than AIMS (including evaluation related to PK):

Period	Visit	Visit Reference	Visit Window
Pre-treatment observation period	Screening	Day 1	–29 to –1
	Baseline	Day 1	–8 to –1
Double-blind Placebo-controlled Period	Start date of treatment	Day 1	–
	W2	Day 15	–7 to +6
	W4	Day 29	
	W6	Day 43	
	At discontinuation of the double-blind placebo-controlled period	Discontinuation date	+3
Double-blind Extension Period	W8	Day 57	–7 to +6
	W12	Day 85	–14 to +13
	W16	Day 113	
	W20	Day 141	
	W24	Day 169	
	W28	Day 197	
	W32	Day 225	
	W36	Day 253	
	W40	Day 281	
	W44	Day 309	
	W48	Day 337	
	At discontinuation of the double-blind extension period	Discontinuation date	+3
Post-treatment observation period	Fu4w	Day 365	+7
	At 4 weeks after discontinuation of study treatment	Discontinuation date +28	

AIMS evaluation:

Period	Visit	Visit Reference	Visit Window
Pre-treatment observation period	Screening	Day 1	–29 to –1
	Baseline	Day 1	–8 to –1
Double-blind Placebo-controlled Period	Start date of treatment	Day 1	–
	W2	Day 15	–7 to +6
	W4	Day 29	
	W6	Day 43	
	At discontinuation of the double-blind placebo-controlled period	Discontinuation date	+3
Double-blind Extension Period	W16	Day 113	–14 to +27
	W32	Day 225	
	W48	Day 337	–14 to +13
	At discontinuation of the double-blind extension period	Discontinuation date	+3
Post-treatment observation period	Fu4w	Day 365	+7
	At 4 weeks after discontinuation of study treatment	Discontinuation date +28	

7.2.2. Allowance of Deviation at the Visit

When tabulating by visit, data that matches the permissible range defined in the section 9.1. Schedule of the protocol is adopted for all the evaluated and measured data. If there are multiple available data within the visit window, the data closer to the visit reference will be adopted. If the number of days from the visit reference is the same, the later data will be adopted.

7.3. Handling of Data for Missing Values

If it becomes impossible to measure or becomes a reference value due to a missing test, a problem with the test sample, or other reasons, the item shall be treated as a missing value and the safety data will not be supplemented. In addition, the efficacy data will not be supplemented unless otherwise specified.

7.4. Handling of Data for AIMS Evaluation Results

If sleeping pills are taken within 8 hours before [redacted] AIMS [redacted] the corresponding AIMS score data will be rejected and will not be used for tabulation.

7.5. Handling of Values of the Quantification Limit or Less of Clinical Laboratory Test

If the continuous values is reported as less than the quantification limit, the quantification limit or less, the quantification upper limit or more, it is used for tabulation by applying the following treatment and is not regarded as a missing value or a zero value.

7.5.1. Case for the Continuous Values Is Reported as Less than the Quantification Limit

The value obtained by adding the following processing to the quantification limit value is used as an alternative value for tabulation.

(1) After confirming the number of significant digits of the corresponding item, subtract 1 from the significant digit of the smallest digit of the reported quantification limit value.
(2) Expand one digit to a smaller place and set 9.

Example)
Report: Less than 3 (significant figures of measurement sits: up to 1st place) ⇒ Handling in tabulation: 2.9
Report: Less than 500 (significant figures of measurement sits: up to 10th place) ⇒ Handling in tabulation: 499

7.5.2. Case for the Continuous Values Is Reported as the Quantification Limit or Less or the Quantification Upper Limit or More

The quantification limit value itself is used as an alternative value for tabulation.
Example)
In the case for below the quantification limit Report: Below 10 ⇒ Handling in tabulation: 10
In the case for above the quantification limit Report: Above 20 ⇒ Handling in tabulation: 20

7.6. Handling of Data Related to Evaluation of Pharmacokinetics

After opening the key code, receive the drug concentration data from the drug concentration measuring institution and consider the handling of the drug concentration data. If there is a deviation from the clinical study protocol, such as that the drug concentration could not be measured or the plasma collection procedure is not followed, the acceptance or rejection of the data will be decided when considering the drug concentration data handling. The considering contents of the data handling shall be kept in record. Less than the lower limit of quantification for drug concentration measurement is written as "N.D." and treated as 0.00 ng/mL. The lower limit of quantification for measuring the plasma concentration of each measurement target is as follows:

- MT-5199 : 1.00 ng/mL
- NBI-98782 : 0.100 ng/mL
- NBI-136110 : 0.200 ng/mL

8. Statistical Methods

8.1. Subjects Registered in the Trial

8.1.1. Subjects Discontinued in the Trial

Population to be analyzed
Subjects randomized to the study drug
Analysis method
In each period of placebo-controlled short-term treatment, long-term exposure and post-treatment observation period, the number of completion / discontinuation and their proportion are tabulated for each treatment group. In each period of placebo-controlled short-term treatment, long-term exposure and extension period, the numbers of subjects and their proportion are tabulated by discontinuation reason. The treatment group in this section are defined as follows:

- Placebo-controlled short-term treatment (only double-blind period)
  - MT-5199 40 mg
  - MT-5199 80 mg
  - All MT-5199 (defined as a pool of 40 mg group and 80 mg group, and so on)
  - Placebo
- Long-term exposure (excluding subjects who are assigned to the placebo group during the double-blind period and are discontinued during the double-blind period)
  - MT-5199 40 mg
  - MT-5199 80 mg
  - MT-5199 80 mg (no dose reduction)
  - All MT-5199
- Post-treatment observation period (only for subjects who completed long-term exposure; those who discontinued treatment are not included in the total)
  - MT-5199 40 mg
  - MT-5199 80 mg
  - MT-5199 80 mg (no dose reduction)
  - All MT-5199

8.1.2. Breakdown of Subjects

Population to be analyzed

Subjects randomized to the study drug

Analysis method

The number of subjects randomized to the study drug, the number of subjects in each analysis set (ITT, PT, safety, and pharmacokinetic) and the number of excluded subjects from each analysis set, and their proportions are summarized for each treatment group. The meanings of the treatment groups in this section are as follows:

- Double-blind period treatment
  - MT-5199 40 mg
  - MT-5199 80 mg
  - All MT-5199
  - Placebo
- Long-term exposure (excluding subjects who are assigned to the placebo group during the double-blind period and are discontinued during the double-blind period)
  - MT-5199 40 mg
  - MT-5199 80 mg
  - MT-5199 80 mg (no dose reduction)
  - All MT-5199
- Post-treatment observation period (only for subjects who completed long-term exposure; those who discontinued treatment are not included in the total)
  - MT-5199 40 mg
  - MT-5199 80 mg
  - MT-5199 80 mg (no dose reduction)
  - All MT-5199

8.1.3. Demographic and the Other Baseline Characteristics

Population to be analyzed

Efficacy analysis set (ITT and PP), safety analysis set and pharmacokinetic analysis set

Analysis method

For each treatment group, items related to major demographic characteristics and disease characteristics at baseline are summarized. The frequency and proportion are shown for the discrete values, and the descriptive statistic is calculated for the continuous values. The meanings of the treatment in this section are as follows:

- Placebo-controlled short-term treatment (only double-blind period)
  - MT-5199 40 mg
  - MT-5199 80 mg
  - All MT-5199
  - Placebo
- Long-term exposure (excluding subjects who are assigned to the placebo group during the double-blind period and are discontinued during the double-blind period)
  - MT-5199 40 mg
  - MT-5199 80 mg
  - MT-5199 80 mg (no dose reduction)
  - All MT-5199

Major demographic characteristics

Item	Explanation	Type
Age	Age at the time of consent acquisition (years)	Continuous
Age category	$< 65, \geq 65$ (2 categories)	Binary
	≥ 65 to $< 75, \geq 75$ (2 categories)	Binary
Gender	Male, Female (2 categories)	Binary
Race	Japanese, the Others (2 categories)	Binary
Ethnicity	Hispanic or Latino, Not Hispanic or Latino (2 categories)	Binary
BMI	BMI (kg/m^2)	Continuous

BMI category	< 18.5, 18.5 to < 25, 25 to < 30, ≥ 30 (4 categories)	Multi-discrete
CYP2D6 Phenotype classification	Ultra-rapid Metabolizer, Extensive Metabolizer, Intermediate Metabolizer, Poor Metabolizer, Not Reported (5 categories)	Multi-discrete
Hepatic function abnormality	No, Yes (2 categories)	Binary

Disease characteristics at baseline

Item	Explanation	Type
Age at TD Diagnosis	Age at TD Diagnosis (years)	Continuous
Duration of TD	< 2, ≥ 2 (2 categories)	Binary
Disease Category	Schizophrenia/Schizoaffective Disorder, Bipolar Disorder/Depressive Disorder (2 categories)	Binary
Age at Disease Diagnosis	of Schizophrenia/Schizoaffective Disorder (years)	Continuous
	of Bipolar Disorder/Depressive Disorder (years)	Continuous
Use of Antipsychotic Medication	No, Yes (2 categories)	Binary
Number of Antipsychotic Medication	1, 2, ≥ 3 (3 categories)	Multi-discrete
Atypical vs Typical Antipsychotic Medication	Atypical only, Typical or both Typical and Atypical (2 categories)	Binary
100 mg CP Equivalent Amount	< 600 mg, ≥ 600 mg (2 categories)	Binary
Use of Anticholinergic Medication	No, Yes (2 categories)	Binary
Suicidality	During Lifetime: No, Yes (2 categories)	Binary
	Within 3 Months: No, Yes (2 categories)	Binary
AIMS total score	AIMS total score (item 1 to 7; central [redacted])	Continuous

8.1.4. Medical History

Population to be analyzed

Safety analysis set

Analysis method

A list of all medical histories collected up to the time of the first dose of the study drug is given using terms coded by MedDRA / J (see Section 8.3 for version).

8.1.5. Status of Pretreatment or Concomitant Medications

Population to be analyzed

Pretreatment drugs are coded using the WHO drug dictionary (version is WHO-DD SEP17B3). A list of concomitants used in combination with the study drug is shown with the following categories.

(1) It has been continued before the first dose of the study drug or is used in combination after the first dose of the study drug

(2) It is used in combination after the first administration date of the study drug and continued until the final evaluation in the follow-up period.

8.1.6. Status in Treatment and Administration of Study Drug

Population to be analyzed

Efficacy analysis set (ITT) and safety analysis set

Analysis methods

The following items are summarized for each treatment group by visit. The frequency and proportion are shown for the discrete values, and the statistical descriptive statistics are calculated for the continuous values.

- The number of days in the treatment period by visits and the entire

- Proportion of study drug administration in the treatment period by visits and the entire (continuous values)
- Proportion of study drug administration in the treatment period by visits and the entire (discrete values; ≥80%, <80%, total)
- Status of dose reduction of study drug by visits (however, long-term exposure only)
- Change classification of study drug administration time throughout the entire period (discrete values; night, others, total)

- Placebo-controlled short-term treatment (only double-blind period)
  - MT-5199 40 mg
  - MT-5199 80 mg
  - ALL MT-5199
  - Placebo
- Long-term exposure (excluding subjects who are assigned to the placebo group during the double-blind period and are discontinued during the double-blind period)
  - MT-5199 40 mg
  - MT-5199 80 mg
  - MT-5199 80 mg (no dose reduction)
  - All MT-5199

8.2. Efficacy Analysis

Analyses are performed using the ITT analysis set by evaluation period. The treatment groups in each evaluation period in this section are as follows:

- Double-blind period
  - MT-5199 40 mg
  - MT-5199 80 mg
  - Placebo

  Extension period (including subjects who are treated as MT-5199 40mg group and 80mg group in the double-blind period in the tabulation)
  - MT-5199 40 mg
  - MT-5199 80 mg
  - MT-5199 80 mg (no dose reduction)
  - MT-5199 80 mg (with dose reduction)

  Post-treatment observation period (only subjects who completed the extension period; excluding subjects who discontinued treatment in the tabulation)
  - MT-5199 40 mg
  - MT-5199 80 mg
  - MT-5199 80 mg (no dose reduction)
  - MT-5199 80 mg (with dose reduction)

8.2.1. Main Analysis

(1) Double-blind period

1) Primary endpoint

- Change from baseline in the AIMS total score (items 1 to 7; central [redacted]) at Week 6 of study treatment

(a) Primary analysis

Each of the MT-5199 groups (MT-5199 40 mg and MT-5199 80 mg groups) is compared with the placebo group through analysis using the mixed-effect model for repeated measures (MMRMs) with the group, underlying disease, and visits (Weeks 2, 4, and 6 of study treatment) as fixed effects, baseline as a covariate, and group × visit and baseline × visit as interactions. The variance-covariance matrix of within-subject scores is unstructured, and the degree of freedom is calculated by the method of Kenward and Roger (1997). Missing values are not imputed. When the model did not converge, another structure of the variance-covariance matrix (ARH (1), AR-1, then CS) is examined, and the model which could confirm the convergence is used.

The following fixed-sequence procedure is followed to control type I family-wise error rate compared to each of the MT-5199 and placebo groups.

- Step 1: The MT-5199 80 mg group is compared with the placebo group. If the result showed a statistical significance, it is proceeded to Step 2.
- Step 2: The MT-5199 40 mg group is compared with the placebo group.

(b) Secondary analysis

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

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

2) Secondary endpoints

- Percentage of subjects with a ≥50% improvement from baseline in the AIMS total score (central [redacted]) at Week 6 of study treatment (AIMS responder)
- Change from baseline in the AIMS total score (items 1 to 7 of items 1 to 12 assessed by investigator [or sub-investigator]) (AIMS total score [site rater]) at Week 6 of study treatment
- CGI-TD score at Week 6 of study treatment

The percentage of AIMS responders at Week 6 of study treatment is 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. A same analysis is also performed on the PP analysis set.

For the change from baseline in the AIMS total score (site rater) at Week 6 of study treatment, MMRM analysis is performed using the total score of items 1 to 7 of items 1 to 12 evaluated by the site rater (or sub-investigator) similar to (a) Primary analysis in 1) Primary endpoint. However, no adjustment for multiplicity is made.

Descriptive statistics for CGI-TD score at Week 6 of study treatment are calculated for each treatment group. Analysis of variance (ANOVA) is performed with the group and underlying disease as fixed effects.

3) Exploratory endpoint

- EQ-5D-5L (Index Value and VAS score)

Descriptive statistics of evaluation values (Index Value and VAS score) and changes from screening at each visit are calculated. ANCOVA analysis is performed with the group and underlying disease as fixed effects and baseline as a covariate.

(2) Extension period to post-treatment observation period

- Change from baseline in AIMS total score (central [redacted])
- Change from baseline in AIMS total score (site rater)

Descriptive statistics and standard errors of the measurement value and the change from baseline of the above 2 AIMS total scores are calculated for each visit during the extension period to post-treatment observation period for each treatment group.

For subjects who are randomized to the placebo group in the double-blind period and then re-randomized in the extension period, descriptive statistics of the assessed AIMS total score (central [redacted]) at each visit during the extension period to the post-treatment observation period and the change from Week 6 of study treatment are also calculated.

The number and percentage of AIMS responders at each visit from the extension period to the post-treatment observation period are calculated for each treatment group.

Descriptive statistics for CGI-TD score at Week 48 of study treatment are calculated for each treatment group.

For EQ-5D-5L (Index Value and VAS score), descriptive statistics of evaluation values (Index Value and VAS score) and changes from screening at each visit are calculated.

8.2.2. Stratified Efficacy Analysis

Population to be analyzed is ITT analysis set.

(1) For the AIMS total score (central [redacted]), the baseline value, the evaluation value at Week 6 of study treatment, and the descriptive statistic of the change from baseline are tabulated for each treatment group in each classification of stratified factors. In addition, the difference between the mean values, the standard errors and the 95% confidence intervals of each treatment group versus the placebo group are calculated. In each stratified factor, draw a forest plot in which the Y-axis is the stratified factor category, and the X-axis is the difference between the groups of the change from baseline (40 mg group vs. placebo group, 80 mg group vs.

placebo group, error length: 95% confidence interval).
If the number of data in any of the treatment groups is less than 5, the 95% confidence interval with that treatment group is not calculated.

(2) For AIMS responders at Week 6 of study treatment, the frequency and proportion of AIMS responders and AIMS non-responders, the number of Missing, and the relative risk (the proportion ratio of AIMS responder in the 40 mg group or 80 mg group to the proportion of the placebo group) and the 95% confidence interval in the relative risk are calculated in each stratified factor classification. In each stratified factor, draw a forest plot in which the Y-axis is the stratified factor category, number of cases in each group of 40 mg and placebo group, number of cases in each group of 80 mg and placebo group, and the X-axis is the relative risk of the AIMS responder (error length: 95% confidence interval in the relative risk). Furthermore, the right part of the figure shows the relative risk of the proportion of the AIMS responder, and the lower and upper limits of the 95% confidence interval.
If the number of data in any of the treatment groups is less than 5, the 95% confidence interval with that treatment group is not calculated.

Stratified Factor and Classification Category

- Underlying Disease : Schizophrenia/Schizoaffective Disorder, Bipolar Disorder/Depressive Disorder
- Gender : Male, Female
- Age Category : $< 65, \geq 65$
- BMI Category : < 18.5, 18.5 to < 25, 25 to $< 30, \geq 30$
- CYP2D6 Phenotype : PM, Non-PM
- TD Duration Category : < 2 years, ≥ 2 years
- Antipsychotic Medication Use at BL : Yes, No
- Number of Antipsychotic Medication at BL : 1, 2, ≥ 3
- Atypical vs Typical Antipsychotic at BL : Atypical only, Typical or both Typical and Atypical
- 100 mg CP Equivalent Amount at BL : < 600 mg, ≥ 600 mg
- Anticholinergic Medication Use at BL : Yes, No
- Suicidality During Lifetime : Yes, No
- Suicidality Within 3 Months : Yes, No

8.2.3. Other Efficacy Analysis

Population to be analyzed is ITT analysis set and summarized by evaluation period.

Excluding AIMS body site scores and CGI-TD

- Double-blind period
  Baseline, Weeks 2, 4, and 6 of study treatment
- Extension period and post-treatment observation period
  Baseline as a reference: Weeks 16, 32, 48, and 52 of study treatment (Follow-up Week 4 after the end of administration)
  Week 6 of study treatment as a reference: Weeks 16, 32, 48, and 52 of study treatment (Follow-up Week 4 after the end of administration)

AIMS body site scores

- Double-blind period
  Weeks 2, 4, and 6 of study treatment
- Extension period and post-treatment observation period
  Weeks 16, 32, 48, and 52 of study treatment (Follow-up Week 4 after the end of administration)

CGI-TD

- Double-blind period
  Week 6 of study treatment
- Extension period and post-treatment observation period
  Weeks 48 and 52 of study treatment (Follow-up Week 4 after the end of administration)

(1) AIMS body site score

Descriptive statistics are calculated for each treatment group for the AIMS body site scores at each visit. Create it for the PP analysis set in the same way.

(2) CGI-TD

The number of subjects at each visit (Weeks 6, 48, and 52 of study treatment) and the frequency and proportion of the number of subjects in each category of CGI-TD are calculated for each treatment group. For the CGI-TD score, the descriptive statistics of evaluation values in Week 52 of study treatment are calculated for each treatment group.

(3) Transition of AIMS total score (central [redacted]) (arithmetic mean)

Create a transition map (error length: standard error, by treatment group) of the arithmetic mean value of the AIMS total score (central [redacted]) at each visit. In addition, a transition map (error length: standard error, by treatment group) of the arithmetic mean value of the change from baseline of the AIMS total score (central [redacted]) at each visit is created.

In the drawing, the double-blind period, extension period and post-treatment observation period are shown in one figure, and the treatment groups are shown so that they can be identified using the following symbols and colors (plots are connected by lines).

Placebo (Day –1 Randomization)	○ black
MT-5199 40mg (Day –1 Randomization)	◆ green
MT-5199 80mg (Day –1 Randomization)	■ red
MT-5199 40mg (Week 6 Placebo Re-randomization)	◇ green
MT-5199 80mg (Week 6 Placebo Re-randomization)	□ red

(4) Transition of AIMS total score (central [redacted]) (MMRM model analysis)

MMRM LS Mean transition chart (error length: standard error, by treatment groups) for the change from baseline of the AIMS total score (central [redacted]) at each visit (Weeks 2 and 4 of study treatment) in the double-blind period is prepared. Create the PP analysis set as the target population in the same way.

(5) Empirical distribution function of AIMS total score (central [redacted])

The cumulative proportion of the number of subjects (by treatment group) to the change from baseline in the AIMS total score (central [redacted]) at Week 6 of study treatment is plotted.

(6) Cumulative contribution percentage of AIMS responders

Plot the cumulative contribution percentage of AIMS responders for the rate of decrease change from baseline in the AIMS total score (central [redacted]) at Week 6 of study treatment.

(7) Maintenance in efficacy

Analysis will be performed on subjects for whom AIMS total score (central [redacted]) data were available at both Week 48 of study treatment and Follow-up Week 4 after the end of administration.

For the AIMS total score (central [redacted]) at Week 48 of study treatment and at Follow-up Week 4 after the end of administration, the descriptive statistic of the of the score from baseline and the frequency and proportion of AIMS responders are calculated for each treatment group.

(8) AIMS total score (site rater)

MMRM is analyzed for the change from baseline of the AIMS total score (site rater, items 1 to 7) at each visit in the double-blind period (Weeks 2 and 4 of treatment).

(9) Relationship between CGI-TD and AIMS total score (central [redacted])

Descriptive statistics of the change from baseline in the AIMS total score (central [redacted]) are shown for each of the following classification categories for CGI-TD at Week 6 of study treatment.

Classification Category 1 (2 categories)
1 or 2 vs. any of from 3 to 7
Classification Category 2 (2 categories)
1 or 2 or 3 vs. any of from 4 to 7

These analyzes are performed by pooling all treatment groups.

8.3. Safety Analysis

Analyses are performed using the safety analysis set. MedDRA Japanese (MedDRA / J) version 23.0 is used to replace adverse events reported by the investigator, and tabulation is performed using the major organ classification (SOC) and preferred term (PT). The frequency and proportion are calculated for the discrete values, and the descriptive statistic is calculated for the continuous values as needed. The treatment group by evaluation period in the safety analysis is defined as follows:

- Placebo-controlled short-term treatment (double-blind period only)
  - MT-5199 40 mg
  - MT-5199 80 mg
  - All MT-5199
  - Placebo
- Long-term exposure (excluding subjects who are assigned to the placebo group during the double-blind period and are discontinued during the double-blind period)
  - MT-5199 40 mg
  - MT-5199 80 mg
  - MT-5199 80 mg (no dose reduction)
  - All MT-5199
- Post-treatment observation period (only for subjects who completed long-term exposure; those who discontinued treatment are not included in the total)
  - MT-5199 40 mg
  - MT-5199 80 mg
  - MT-5199 80 mg (no dose reduction)
  - All MT-5199

8.3.1. Adverse Events

8.3.1.1. Summary

The number of subjects in which the following adverse events were observed at least once (hereinafter referred to as the number of subjects with the adverse event) and the incidence are summarized for each treatment group by evaluation period.

- Adverse event (AE)
- Adverse drug reaction (ADR) (AE for which a causal relationship with the study drug was evaluated as reasonable)
- Serious AE
- Serious ADR
- AE leading to discontinuation of study drug
- ADR leading to discontinuation of study drug
- AE leading to dose reduction
- ADR leading to dose reduction
- AE leading to death

8.3.1.2. Tabulation by SOC / PT

For the following adverse events (excluding adverse events of special interest [AESI]), the total number of subjects and the incidence of individual adverse events and those classified by SOC and PT are tabulated for each treatment group by evaluation period.

Regarding AESI, the total number of subjects and the incidence of AESI and individual adverse events and those classified by PT are tabulated for each treatment group by evaluation period.

The display order (excluding AESI) is the order of international agreement for SOC and the descending order of the number of subjects in All MT-5199 (in the case of the same number, the ascending order of PT code). AESI are in ascending order of the list shown in Appendix 13.3, and PT is in descending order of the number of subjects in All MT-5199 (in the case of the same number, PT code ascending order).

- AE (all)
- AE (2% or more in ALL MT-5199 group)
- ADR (all)

- ADR (2% or more in ALL MT-5199 group)
- Serious AE
- Serious ADR (however, the post-treatment observation period is excluded)
- AE leading to discontinuation of study drug
- ADR leading to discontinuation of study drug
- AE leading to dose reduction
- ADR leading to dose reduction
- AE of Special Interest (see attached sheet for PT list)
- ADR of Special Interest (see attached sheet for PT list)
- Serious AE of Special Interest (see attached sheet for PT list)
- AE of Special Interest leading to discontinuation of study drug (see attached sheet for PT list)
- AE of Special Interest leading to dose reduction (see attached sheet for PT list)
- AE leading to death

8.3.1.3. Tabulation by Severity

The incidence of adverse events by severity (severe, moderate, mild) is tabulated by the method and format according to 8.3.1.2. Tabulation by SOC / PT. The aggregation method for each severity is as follows:

(1) In the case that adverse events of different severities occur in the same subject, the worst severity is counted as one person.

(2) In the case that multiple adverse events of the same severity occur in the same subject, it is counted as one person at that level.

(3) In the case that multiple same adverse events occur in the same subject, the worst severity is counted as one person.

8.3.1.4. Tabulation by Onset Time

The incidence of adverse events for each of the following onset time categories is tabulated by the same method and format as in 8.3.1.2. Tabulation by SOC / PT (however, long-term exposure only).

Onset time categories:

Day 1 to Week 6, Week 6 to Week 12, Week 12 to Week 24, Week 24 to Week 36, Week 36 to Week 48, and Week 12 to Week 48 of treatment

Week X to Week Y: Adverse events that occurred from the day after the Week X survey day to the Week Y survey day.

8.3.1.5. Incidence Rate of Adverse Events According to the Person-year Exposure Method

For adverse events and serious adverse events, the total exposure person-year is shown for each treatment group, and tabulation is made according to the method and format in 8.3.1.2. Tabulation by SOC / PT (however, long-term exposure only).

- Person-year incidence rate (by treatment group, by SOC / PT)
  (Total number of adverse events occurring by SOC / PT) / (total exposure person-year) × 100
- Total exposure person-year (by treatment group)
  Total number of treatment days for subjects (year)

8.3.1.6. Stratified Safety Analysis

The number of subjects and the incidence of adverse events in each of the following stratified factor classifications are tabulated for each treatment group by evaluation period (however, excluding the post-treatment observation period).

In addition, the incidence of AEs and AESIs is tabulated for each stratified factor classification in the same manner and format as in 8.3.1.2. Tabulation by SOC / PT (however, excluding the post-treatment observation period).

Stratified Factor and Classification Category

- Underlying Disease : Schizophrenia/Schizoaffective Disorder, Bipolar Disorder/Depressive Disorder
- Gender : Male, Female
- Age Category : $< 65, \geq 65$

- BMI Category : < 18.5, 18.5 to < 25, 25 to < 30, ≥ 30
- CYP2D6 Phenotype : PM, Non-PM
- Hepatic Function Abnormality : Yes, No
- Antipsychotic Medication Use at BL : Yes, No
- Atypical vs Typical Antipsychotic at BL : Atypical only, Typical or both Typical and Atypical
- Suicidality During Lifetime : Yes, No
- Suicidality Within 3 Months : Yes, No

8.3.2. Laboratory Test

The continuous values of hematological tests and blood biochemical tests (see 3.2.1.3. Examination / Observation Items) at each visit, and the descriptive statistics of the change from baseline are tabulated for each treatment group by evaluation period (from baseline to Week 6 of treatment, and from baseline to Week 52 of treatment excluding Follow-up Week 4 after discontinuation). In addition, for urinalysis of qualitative tests (see 3.2.1.3. Examination / Observation Items), a shift table of changes at each visit based on the baseline category is displayed for each evaluation period (from baseline to Week 6 of treatment, and from baseline to Week 52 of treatment excluding Follow-up Week 4 after discontinuation).

8.3.2.1. Frequency Aggregation by Criteria for Assessing Clinically Significant Abnormalities

The number and proportion of subjects with abnormalities that meet the following criteria after administration of the study drug are calculated for each treatment group by evaluation period (from baseline to Week 6 of treatment, and from baseline to Week 48 of treatment).

Criteria for assessing clinically significant abnormalities in this study (laboratory test)

- White blood cell count < 2800/mm^3
- Neutrophils count < 1500/mm^3
- ALT > 3 × ULN
- AST > 3 × ULN
- Total bilirubin > 1.5 × ULN
- γ-GTP > 3 × ULN
- Urea nitrogen > 30 mg/dL
- Serum creatinine > 1.5 × (BL value), or 1.5 × ULN
- CPK > 5 × ULN

8.3.3. Vital Signs

Descriptive statistics of vital signs (see 3.2.1.3. Examination / Observation Items) at each visit and changes from baseline are shown for each treatment group by evaluation period (from baseline to Week 6 of treatment, and from baseline to Week 52 of treatment excluding Follow-up Week 4 after discontinuation).

8.3.3.1. Frequency Tabulations by criteria for Assessing Clinically Significant Abnormalities

The number and proportion of subjects with abnormalities that meet the following criteria after administration of the study drug are calculated for each treatment group by evaluation period (from baseline to Week 6 of treatment, and from baseline to Week 48 of treatment).

Criteria for assessing clinically significant abnormalities in this study (vital signs)

- Systolic blood pressure < 90 mmHg and decrease from baseline value ≥ 20 mmHg
- Systolic blood pressure > 180 mmHg and increase from baseline value ≥ 20 mmHg
- Diastolic blood pressure < 50 mmHg and decrease from baseline value ≥ 10 mmHg
- Diastolic blood pressure > 105 mmHg and increase from baseline value ≥ 10 mmHg
- Pulse rate < 50 bpm and decrease from baseline value ≥ 15 bpm
- Pulse rate > 120 bpm and increase from baseline value ≥ 15 bpm

8.3.4. 12-lead ECG

The continuous values of 12-lead ECG parameters (see 3.2.1.3. Examination / Observation Items) and the descriptive statistics of the change from baseline are calculated for each treatment group by evaluation period (however, excluding post-treatment observation period). In addition, the tabulated results for each visit of 12-lead ECG findings are calculated for each treatment group by evaluation period (from baseline to Week 6 of treatment, and from baseline to Week 52 of treatment excluding Follow-up Week 4 after discontinuation).

8.3.4.1. Categorical Data Analysis

The number of subjects whose maximum QTcF value after administration of the study drug and the maximum value of the change from baseline in QTcF and their proportions respectively are tabulated for each treatment group by evaluation period (from baseline to Week 6 of treatment, and from baseline to Week 52 of treatment).

- QTcF: > 450 msec, > 480 msec, > 500 msec
- Change from baseline in QTcF: >30 msec, > 60 msec

8.3.5. Psychiatric Symptomatology Assessment Scales

8.3.5.1. Psychiatric Symptomatology Assessment Scales except for C-SSRS

SAS (Global score), BARS (Total score, Global score), MMSE-J (Total score), JCDSS (Total score), PANSS (Positive score, Negative score, General Psychopathology, Composite Scale), MADRS-J (Total score) and YMRS (Total score) at each visit and the change from baseline for each treatment group by evaluation period (from baseline to Week 6 of treatment, and from baseline to Week 52 of treatment excluding Follow-up Week 4 after discontinuation). Also, plot the transition of each item (Arithmetic Mean ± SEM).

8.3.5.2. C-SSRS

(1) At each visit, the frequency and proportion of the number of subjects who answered yes for suicidal ideation and each question (questions 1 to 5), suicide attempt and each question (questions 6 to 10), suicidal ideation or suicide attempt are summarized for each treatment group by evaluation period (from baseline to Week 6 of treatment, and from baseline to Week 52 of treatment). However, subjects with baseline values (both items of During Lifetime and Within 3 Months) are included.

(2) Regarding the suicidal ideation score (scores 0 to 5), the shift table of the maximum value in each evaluation period with respect to the reference visit is shown for each treatment group by evaluation period (combination of 1) to 3) below).
   1) Reference visit: Past 3 month; Evaluation period: Day 1 through Week 6
   2) Reference visit: Past 3 month; Evaluation period: Day 1 through Week 48
   3) Reference visit: Week 48; Evaluation period: After Week 48 through Week 52 (only for subjects who completed treatment)

8.3.5.3. AE related to Suicide Events

Create a listing for the following items:

- Subject identification code, age, gender, MedDRA preferred terms, severity, action taken for the investigational product, seriousness, baseline C-SSRS assessment (Suicidal Ideation Yes / No and Suicidal Attempt Yes / No for the assessment during lifetime and within 3 months prior to assessment)

8.4. Pharmacokinetic Analysis

Analyses are performed in the pharmacokinetic analysis set.

Descriptive statistics (number of subjects, mean, SD, 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 are calculated by treatment group for each scheduled blood sampling time point. The average elapsed time from the most recent administration to blood sampling time point is calculated for each treatment group at each scheduled blood sampling time point.

Graphs are prepared for the concentrations of unchanged drug (MT-5199) and metabolites (NBI-98782 and NBI-136110) in plasma at each time point of blood sampling, with the time elapsed from the most recent administration to the time of blood sampling as the horizontal axis and the plasma concentration as the vertical axis. Both the graphs plotted for each treatment group and the graphs plotted for the MT-5199 40 mg and MT-5199 80 mg groups on the same graph are created. Symbols to be plotted are classified by CYP2D6 phenotypes (non-PM and PM).

8.5. Pharmacodynamic Analysis

Not applicable.

9. Numerical Description

9.1. Number of Displayed Digits

(1) Subject Demographics, Efficacy and Safety Analysis

1) The p-value is displayed with 3 digits after the decimal point. However, if it is less than 0.001, it is written as "<0.001."

2) The proportion (percentage value) is displayed as an integer part + one digit after the decimal point.

3) Descriptive statistics (minimum, maximum) are displayed with the same number of digits as the original variable.

4) Descriptive statistics (mean, standard deviation, median), LS Mean, and standard error are displayed as the number of digits of the original variable + 1 digit.

(2) Pharmacokinetic Analysis

The number of display digits of the mean, standard deviation, minimum, median, and maximum is displayed with 3 significant figures. Rounding is rounded off.

1) The number of subjects is displayed as an integer.

2) Use natural logarithm for logarithm conversion.

10. Changes in the Analysis Plan from the Protocol

Although MMRM was planned to be performed for the CGI-TD score at Week 6 of study treatment, the analysis model was changed to ANOVA because the visit of the CGI-TD score in the double-blind period is at Week 6 of study treatment only and MMRM was not applicable.

11. Software Used

The application to be used and its version are as follows:

- Windows SAS (release 9.4)

12. References

Not applicable.

13.Appendix

13.1. Antipsychotic Drugs

In the list of antipsychotic drugs used in this clinical trial, the antipsychotic drug classification and the chlorpromazine (CP) equivalent amount are shown.

Preferred Term	Route	Frequency	Antipsychotic Drug Classification	100 mg CP Equivalent Amount
ARIPIPRAZOLE	Intramuscular	Every month	Atypical	100
ARIPIPRAZOLE	Intramuscular	Once four weeks	Atypical	100
ARIPIPRAZOLE	Intramuscular	Once a month	Atypical	100
ARIPIPRAZOLE	Intramuscular	Once in 4 weeks	Atypical	100
ARIPIPRAZOLE	Intramuscular	Every 4 weeks	Atypical	100
ARIPIPRAZOLE	Oral		Atypical	4
ASENAPINE	Oral		Atypical	2.5
ASENAPINE MALEATE	Oral		Atypical	2.5
ASENAPINE MALEATE	Other		Atypical	2.5
BLONANSERIN	Oral		Atypical	4
BREXPIPRAZOLE	Oral		Atypical	1
BROMPERIDOL	Oral		Typical	2
CHLORPROMAZINE HYDROCHLORIDE	Oral		Typical	100
CHLORPROMAZINE HYDROCHLORIDE	Oral	QID	Typical	100
CLOZAPINE	Oral		Atypical	50
FLUPHENAZINE DECANOATE	Intramuscular	Every month	Typical	15
FLUPHENAZINE DECANOATE	Intramuscular	Every 4 weeks	Typical	15
HALOPERIDOL	Oral		Typical	2
HALOPERIDOL DECANOATE	Intramuscular	Every 4 weeks	Typical	30
HALOPERIDOL DECANOATE	Intramuscular	Every month	Typical	30
HALOPERIDOL DECANOATE	Intramuscular	Once a month	Typical	30
HALOPERIDOL DECANOATE	Oral		Typical	2
LEVOMEPROMAZINE	Oral		Typical	100
LEVOMEPROMAZINE MALEATE	Oral		Typical	100
MOSAPRAMINE HYDROCHLORIDE	Oral		Typical	33
OLANZAPINE	Oral		Atypical	2.5
OXYPERTINE	Oral		Typical	80
PALIPERIDONE	Oral		Atypical	1.5
PALIPERIDONE PALMITATE	Intramuscular	Once every 4 weeks	Atypical	18.75
PALIPERIDONE PALMITATE	Intramuscular	Once a month	Atypical	18.75
PALIPERIDONE PALMITATE	Intramuscular	4Week	Atypical	18.75
PALIPERIDONE PALMITATE	Intramuscular	Every 4 weeks	Atypical	18.75

Preferred Term	Route	Dosage	Antipsychotic Drug Classification	100 mg CP equivalent amount (mg)
PALIPERIDONE PALMITATE	Intramuscular	Every month	Atypical	18.75
PALIPERIDONE PALMITATE	Intramuscular	Monthly	Atypical	18.75
PALIPERIDONE PALMITATE	Intramuscular	Once in four weeks	Atypical	18.75
PERICIAZINE	Oral		Typical	20
PEROSPIRONE	Oral		Atypical	8
PEROSPIRONE HYDROCHLORIDE	Oral		Atypical	8
QUETIAPINE	Oral		Atypical	66
QUETIAPINE	Oral	4times par day	Atypical	66
QUETIAPINE FUMARATE	Oral		Atypical	66
RISPERIDONE	Intramuscular	1/2 weeks	Atypical	10
RISPERIDONE	Intramuscular	Every two weeks	Atypical	10
RISPERIDONE	Oral		Atypical	1
RISPERIDONE	Oral	QID	Atypical	1
SULPIRIDE	Oral		Typical	200
TIAPRIDE	Oral		Typical	100
TIAPRIDE HYDROCHLORIDE	Oral		Typical	100
TIAPRIDE HYDROCHLORIDE	Oral	QID	Typical	100
ZOTEPINE	Oral		Atypical	66

URL: Community Mental Health & welfare Bonding Organization Home Page
https://www.comhbo.net/?page_id=4370

13.2. EQ-5D-5L Score Conversion Table (Japanese)

A score created by a group of Japanese researchers (Ikeda et al.) and approved by the EuroQol headquarters as the EQ-5D Japanese version (5-step version), which will be used for research.

State	Score	State	Score
11111	1.000	:	:
11112	0.867	55542	0.159
11113	0.829	55543	0.120
11114	0.771	55544	0.062
11115	0.743	55545	0.034
11121	0.895	55551	0.171
11122	0.823	55552	0.099
11123	0.784	55553	0.060
11124	0.726	55554	0.002
:	:	55555	-0.025

Shunya IKEDA, et. al. "Developing a Japanese version of the EQ-5D-5L value set" J. Natl. Inst. Public Health, 64(1): 47-55, ,2015
Presented URL: From the homepage of Community Mental Health & Welfare Bonding Organization (https://www.comhbo.net/?page_id=4370)

13.3. The Types of Adverse Events of Special Interest (AESI)

The corresponding PT code is shown in the attached document. (*Top Line Data).

#	AESI Group Name	Extraction Condition	Note
1*	Somnolence (9 PTs)	Somnolence, Sedation, Fatigue, Asthenia, Lethargy, Malaise, Hypersomnia, Sedation complication, Decreased activity	Important Identified Risks
2	Hypersensitivity (435 PTs)	Anaphylactic/anaphylactoid shock conditions (SMQ), Anaphylactic reaction (SMQ), Hypersensitivity (SMQ), Angioedema (SMQ), Drug reaction with eosinophilia and systemic symptoms syndrome (SMQ), Severe cutaneous adverse reactions (SMQ), Erythema	Important Identified Risks
3*	Parkinsonism (41 PTs)	Parkinson-like events (SMQ), Salivary hypersecretion	Important Identified Risks
4*	Depression or Suicidality (96 PTs)	Depression (excl. suicide and self-injury) (SMQ), Suicide/self-injury (SMQ)	Important Potential Risks
5	Cardiac events and QT prolonged (29 PTs)	Cardiac failure, Chest pain, Myocardial infarction, Torsade de pointes/QT prolongation (SMQ), Death, Myocardial ischaemia	Important Potential Risks
6	Hyperprolactinemia (3 PTs)	Blood prolactin increased, Galactorrhoea, Menstruation irregular	Important Potential Risks
7	Confusional state (3 PTs)	Confusional state, Mental status changes, Encephalopathy	Important Potential Risks
8	Akathisia (8 PTs)	Akathisia, Extrapyramidal disorder, Hyperkinesia, Hyperkinesia neonatal, Motor dysfunction, Movement disorder, Psychomotor hyperactivity, Restlessness, Restless legs syndrome	Adverse events that may be directly related to monoamine depletion
9	Anxiety (1 PT)	Anxiety	Adverse events that may be directly related to monoamine depletion
10	Worsening of Underlying Psychiatric Condition (20 PTs)	Suicidal ideation, Depression, Bipolar I disorder, Depressed mood, Depressive symptom, Hostility, Irritability, Mania, Paranoia, Psychotic disorder, Schizophrenia, Schizoaffective disorder, Suicide attempt, Mood swings, Suicidal behaviour, Post-traumatic stress disorder, Bipolar disorder, Major depression, Intentional self-injury, Hypomania	Potential Risks of TD patients
11	Dysphagia (2 PTs)	Dysphagia, Oesophageal food impaction	Adverse events related to TD symptoms, coordinating physician opinions
12	Hepatotoxicity (322 PTs)	Cholestasis and jaundice of hepatic origin (SMQ), Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ), Hepatitis, non-infectious (SMQ), Liver neoplasms, benign (incl cysts and polyps) (SMQ), Liver malignant tumours (SMQ), Liver tumours of unspecified malignancy (SMQ), Liver related investigations, signs and symptoms (SMQ), Liver-related coagulation and bleeding disturbances (SMQ)	General risks Drug-induced risks
13	Malignant syndrome (3 PTs)	Neuroleptic malignant syndrome (SMQ)	
14	Hypotension/orthostatic hypotension (9 PTs)	Blood pressure decreased, Dizziness, Dizziness postural, Fall, Hypotension, Orthostatic hypotension, Orthostatic intolerance, Presyncope, Syncope	
15	Cognitive disorder (2 PTs)	Disturbance in attention, Cognitive disorder	Requested by PMDA

Addendum

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

(A Confirmatory Trial and the Long Term Exposure Trial)

Protocol No.	MT-5199-J02

Addendum date	December 11, 2020
Addendum author	[redacted]

Target document	Statistical Analysis Plan
Version No.	1
Signature date	November 12, 2020

In the protocol of 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 (A Confirmatory Trial and the Long Term Exposure Trial), the following analysis items are added to the statistical analysis plan (version 1.0).

Corresponding part	Contents of addendum
8.2. Efficacy Analysis	8.2.3. Other Efficacy Analysis (3) Transition of AIMS total score (central [redacted]) (arithmetic mean) Create a transition map (error length: standard error, by treatment groups) of the arithmetic mean value of the AIMS total score (central [redacted]) at each visit. In addition, a transition map (error length: standard error, by treatment groups) of the arithmetic mean value of the change from baseline of the AIMS total score (central [redacted]) at each visit is created. In the drawing, the double-blind period, extension period and post-treatment observation period are shown in one figure, and the treatment groups are shown so that they can be identified using the following symbols and colors (plots are connected by lines). Also create the corresponding table. Placebo (Day –1 Randomization) ○ black MT-5199 40mg (Day –1 Randomization) ◆ green MT-5199 80mg (Day –1 Randomization) ■ red MT-5199 40mg (Week 6 Placebo Re-randomization) ◇ green MT-5199 80mg (Week 6 Placebo Re-randomization) □ red
	(Reason) The summary statistics calculation table corresponding to the plot after Week 6 in Figure 14.2.1.2 was not created, so it was added.