A Placebo-controlled Study of MD-120 in Depression Patients

Statistical Analysis Plan

Mochida Pharmaceutical Co., Ltd.

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Version History

Version	Date Created or Amended	Reasons for Amendments	Prepared By	Comment
1.0	2020/4/1	-	[redacted]	Initial version
2.0	2022/9/14	Refer to revision history	[redacted]	Finalized

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Definition of Terms

The definitions of the main terms used in this SAP are as follows.

Term	Description
Analysis Data set	See the GCP SOPs [redacted]
CMH test	Abbreviation for Cochran-Mantel-Haenszel test.
FAS	Abbreviation for Full Analysis Set.
GEE analysis	Abbreviation for analysis using Generalized Estimating Equations.
Handling plan	See the GCP SOPs [redacted]
IWRS	Abbreviation for Interactive Web Response System.
LOCF	Abbreviation for Last Observation Carried Forward. One way to impute missing data. An imputation method that replaces missing data with the last observed value.
MAR	Abbreviation for Missing At Random. A missing mechanism that the probability of being missing at a given time point is related to the value of the endpoint observed at a previous time point.
MCMC method	Abbreviation for Markov-Chain Monte Carlo method.
MMRM analysis	Abbreviation for analysis using Mixed-effects Model for Repeated Measures.
Monotone missing	Missing patterns that an endpoint is observed up to a certain time point, but missing at later time points.
Non-monotone missing	Missing patterns that an endpoint is missing at once but is observed again at a later time point.
OC	Abbreviation for Observed Cases. Refers to not imputing.
PPS	Abbreviation for Per Protocol Set.
PT	Abbreviation for Preferred Term in MedDRA.
SAS	Abbreviation for Statistical Analysis System. Software used for analysis.
SOC	Abbreviation for System Organ Class in MedDRA.
Tipping Point Analysis	A method of sensitivity analysis for missing mechanisms.

1 Study Director and Team

1.1 Study Director

[redacted]

1.2 Person Responsible for Monitoring

[redacted]

1.3 Person Responsible for Statistical Analysis

[redacted]

1.4 Person Responsible for Data Management

[redacted]

1.5 Person Responsible for Safety Information Management

[redacted]

1.6 Person Responsible for pharmacokinetic analysis

[redacted]

1.7 Statistical Analysis Team

[redacted]

2 Objectives, Eligible Subjects and Study Design

2.1 Study Objective

To verify the efficacy and evaluate the safety of 8-week once-daily oral administration of MD-120 (50 mg and 100 mg) in Japanese patients with depression.

2.2 Eligible Subject

Patients with depression

2.3 Study Drug

Investigational drug

- MD-120 50 mg tablet

Comparator

- Placebo tablet

2.4 Treatment group

MD-120 50 mg group

MD-120 100 mg group

Placebo group

2.5 Study Design

A randomized, parallel-group, multicenter, double-blind, placebo-controlled study

2.6 Target Sample Size and Rationale for Selection of Sample Size

2.6.1 Target Sample Size

594 subjects as FAS (198 subjects per group)

2.6.2 Sample Size Rationale

[redacted]

[redacted]

3 Analysis Sets

3.1 Efficacy Analysis Population

3.1.1 FAS

Of subjects registered for randomization, those meeting all the following items will be included in the above analysis set.

(1) Subjects who have received the investigational drug at least once during treatment period
(2) Subjects who have evaluated for the total MADRS score at the baseline and at least one timepoint after the start of treatment period

3.1.2 PPS

Of subjects included in the FAS, those meeting all the following items will be included in the per protocol set (PPS).

(1) Subjects who meet the inclusion criteria and do not fall under the exclusion criteria
(2) Subjects who have not violated the Protocol “7.1.1 Prohibited concomitant drugs“ or the Protocol “7.1.2 Prohibited concomitant therapies“ from the start of screening period to the end of treatment period
(3) Subjects who have used hypnotic/sedative drugs in compliance with provisions in the Protocol “7.1.3 Allowed concomitant drugs“ from the start of screening period to the end of treatment period
(4) Subjects in whom the study treatment period or the number of days from the first dose of the investigational drug to the last dose in the treatment period is 42 days or longer, and the drug-use rate during the study treatment period is 75% or higher

3.2 Safety Analysis Population

3.2.1 Safety analysis set in the run-in period (SAF in the run-in period)

Subjects meeting all the following items will be included in the above analysis set.

(1) Subjects who have received the investigational drug at least once during run-in period
(2) Subjects in whom the safety evaluation data in the run-in period are available

3.2.2 Safety analysis set in the treatment period (SAF)

Of subjects registered for randomization, those meeting all the following items will be included in the above analysis set.

(1) Subjects who have received the investigational drug at least once during treatment period
(2) Subjects in whom the safety evaluation data after the dose of the investigational drug in the treatment period are available

3.2.3 Safety analysis set in the follow-up period (SAF in the follow-up period)

Subjects meeting all the following items will be included in the above analysis set.

(1) Subjects included in the "Safety analysis set in the treatment period"

(2) Subjects in whom the safety evaluation data in the follow-up period are available

3.3 Other Analysis Population

3.3.1 Pharmacokinetic analysis set

Subjects meeting all the following items at the same time will be included in the above analysis set.

(1) Subjects who have received the investigational drug at least once during treatment period

(2) Subjects in whom the drug concentration evaluation data after the dose of the investigational drug in the treatment period are available

4 Data Used in Analysis

4.1 Analysis Data Set

4.1.1 Format of Analysis Data Set

SAS data set

4.1.2 Contents of the Analysis Data Set

(1) Data reflecting subject and data handling performed in accordance with the Handling Plan, and conforming to GCP SOPs [redacted]
- CRF data (including eCOA data)
- Laboratory Tests data

(2) Analysis population flags and reasons for exclusion

(3) Concomitant Drug Code (WHO-DDs)

(4) Concurrent Diseases and Adverse Event Codes (MedDRA)

(5) Protocol Deviation Case Data

(6) Other data and flags required for analysis
- Flags for sample abnormalities
- Flags for AEs of Interest
- Inclusion/Exclusion criteria data (IWRS data)

4.2 Data Sets Other Than the Analysis Data Set

4.2.1 Data Sets Obtained before Unblinding

Not applicable

4.2.2 Data Sets Obtained on or after Unblinding

(1) Key data
- Received from the person responsible for Study Drug Allocation

(2) Drug concentration data
- Received from the person responsible for pharmacokinetic analysis

5 Assessment Time

5.1 Assessment Time Definitions

5.1.1 Assessments by Time Point

The following table shows each assessment time points for the parameters assessed.

Assessment Time	Definition
Start of screening period, End of screening period, Start of run-in period (no visit), End of run-in period or the time of premature termination, Week 1 visit during treatment period, …, Week 8 visit during treatment period, …, Week 8 visit during treatment period or the time of premature termination, Week 1 visit during follow-up period, Week 1 visit during follow-up period or the time of premature termination, End of follow-up period or the time of premature termination	See the protocol

For convenience, the assessment time points shown above are replaced as follows.

Assessment Time (before replacing the terms)	Assessment Time (after replacing the terms)
End of run-in period or the time of premature termination	Baseline
Week 1,..., Week 8 visit during treatment period	Week 1,..., Week 8
Week 8 visit during treatment period or the time of premature termination	End of treatment period (EOT)
Week 1 visit during follow-up period	Follow-up Week 1

5.1.2 Assessments by period

The assessment time of the items to be evaluated for each period shows as follows.

Evaluation period	Definitions
Screening period	Period from the start of any observation or test scheduled at the initial registration to the second registration. Period when the subject eligibility is reviewed.

Run-in period	Period from the next day of the second registration to the day of randomization or the time of completion of all observation and tests scheduled at the visit at the time of premature termination. Period when the subject's stability of symptom and compliance are checked.
Treatment period	Period from the next day of randomization to the day of the Week 8 visit during treatment period or the visit at the time of premature termination. Period when the efficacy and safety are evaluated.
Follow-up period	Period from the next day of the Week 8 visit during treatment period or the next day of the visit at the time of premature termination to the time of completion of all observation and tests scheduled at completion or the visit at the time of premature termination during follow-up period*. Period when the post-treatment safety is evaluated. * The time of premature termination after Week 1 visit during follow-up period.

5.1.3 Assessments Not Dependent on the Time Point or period

When analyses are to be performed throughout the entire term of the study (e.g., analysis of survival data, laboratory abnormalities), all data including unscheduled measurements will be used for the analysis unless otherwise specified.

5.2 Handling of Data

The handling of the data for each endpoint is defined in the Handling Plan. This section defines the handling of data not described in the Handling Plan.

5.2.1 Assessments Performed for Each Time Point

Not applicable

5.2.2 Assessments Performed for Each period

5.2.2.1. Handling of Adverse Events

This should be handled based on onset date of adverse events according to Section 5.1.2.

5.2.2.2. Handling of withdrawal

This should be handled according to the CRF.

6 Definition of Prognostic Factors (Explanatory Variables)

The definitions of prognostic factors is as follows. Otherwise, the definitions are defined separately for each analysis item. For details, see Appendix 1.

6.1 Background Factors

6.1.1 Demographic variables

(1) Sex

(2) Race

(3) Age (years)

- Age at informed consent

(4) Height (cm)

(5) Body weight (kg) (at the start of the screening period)

(6) BMI (kg/m^2) (at the start of the screening period)

- Body weight (kg) (at the start of the screening period) / (height (cm) / 100) ^{2}

6.1.2 Other factors

(1) Age at the onset of depression (year)

- Age at the date of depression*

*: Definition of the date of onset of depression

- If the day of *time of onset of depression* is missing then impute the missing part as 15th.
- If the month and the day of *time of onset of depression* is missing then impute the missing part as July, 1st.

(2) Period from onset of depression (month)

- (Date of informed consent - Date of onset of depression) / 30
  However, if it becomes negative, it is replaced with 0

(3) Number of depressive episodes (times)

(4) Duration of current depressive episode (month)

- (Date of informed consent - date of onset of the current depressive episode*) / 30

If it becomes negative, it is replaced with 0

* Impute the day of *the time of onset of depression* as 15th.

(5) Presence/absence of prior treatment with antidepressant drugs for current and past depressive episodes

(6) Presence/absence of concomitant use of hypnotic/sedative drugs and narcoleptics (within 2 months before the initial registration)
(7) Presence/absence of a history of treatment with antianxiety drug (within 2 months before the initial registration)
(8) Presence or absence of comorbidities

6.1.3 Baseline

(1) Total MADRS score (baseline)
(2) Total HAMD17 score (baseline)
(3) CGI-S (baseline)
(4) Total $QIDS_{16}$-SR-J score (baseline)
(5) Total SDS score (baseline)

6.2 Covariates measured after randomization

6.2.1 Extent of Exposure to the investigational drug

(1) Duration of exposure of the investigational drug (days) (treatment period)
- date of the last dose of the investigational drug in the treatment period - date of the first dose of the investigational drug in the treatment period + 1

(2) Compliance rate of the investigational drug (%) (treatment period)
- Total number of tablets taken from Week 1 to EOT (tablets) / [duration of exposure of the investigational drug (days) (treatment period)× 2] × 100

(3) Total exposure of the investigational drug (mg) (treatment period)
- Placebo group: 0
- MD-120 50 mg group: Total number of tablets taken from Week 1 to EOT × 25
- MD-120 100 mg group: Number of tablets taken on Week 1 × 25 + Total number of tablets taken from Week 2 to EOT × 50

  ※When the subject discontinued before Week 1, Total number of tablets taken on EOT × 25

6.2.2 Concomitant Drugs and Therapies

Not applicable

7 Endpoint (dependent variable) Definitions

Missing data will be handled as follows.

- Imputation rules of Efficacy endpoints are defined individually.
- Others will not be imputed in principle. If specific imputation rules are defined for individual endpoints, they will be imputed accordingly.

7.1 Efficacy endpoints

7.1.1 Total MADRS score

(1) Definition of a formula or derivation

- Sum of MADRS 10 items

(2) Assessment time

- Baseline, Week 1, 2, 4, 6, and 8

(3) Imputation method

- If imputing missing values, LOCF method will be used

7.1.2 Change in total MADRS score from baseline

(1) Definition of a formula or derivation

- Total MADRS score at each time point - total MADRS score (Baseline)

(2) Assessment time

- Week 1, 2, 4, 6, and 8

(3) Imputation method

- If imputing missing values, LOCF method will be used

7.1.3 Response evaluated by total MADRS score

(1) Definition of a formula or derivation

- Response if the total MADRS score at each time point is ≤50% from baseline score

(2) Assessment time

- Weeks 1, 2, 4, 6, and 8

(3) Imputation method

- If imputing missing values, LOCF method will be used (only at Week 8)

7.1.4 Remission evaluated by total MADRS score

(1) Definition of a formula or derivation

- Remission if the total MADRS score at each time point is ≤10

(2) Assessment time

- Weeks 1, 2, 4, 6, and 8

(3) Imputation method

- If imputing missing values, LOCF method will be used (only at Week 8)

7.1.5 Total HAMD17 score

(1) Definition of a formula or derivation

- Sum of HAMD 17 items

(2) Assessment time

- Baseline, Week 2, 4, and 8

(3) Imputation method

- If imputing missing values, LOCF method will be used

7.1.6 Change in total HAMD17 score from baseline

(1) Definition of a formula or derivation

- Total HAMD17 score at each time point - total HAMD17 score (Baseline)

(2) Assessment time

- Week 2, 4, and 8

(3) Imputation method

- If imputing missing values, LOCF method will be used

7.1.7 Response evaluated by total HAMD17 score

(1) Definition of a formula or derivation

- Response if the total HAMD17 score at each time point is ≤50% from baseline score

(2) Assessment time

- Week 2, 4, and 8

(3) Imputation method

- If imputing missing values, LOCF method will be used (only at Week 8)

7.1.8 Remission evaluated by total HAMD17 score

(1) Definition of a formula or derivation

- Remission if the total HAMD17 score at each time point is ≤7

(2) Assessment time

- Week 2, 4, and 8

(3) Imputation method

- If imputing missing values, LOCF method will be used (only at Week 8)

7.1.9 CGI-I

(1) Definition of a formula or derivation

- Measured values will be used.

(2) Assessment time

- Week 1, 2, 4, 6, and 8

(3) Imputation method

- If imputing missing values, LOCF method will be used (only at Week 8)

7.1.10 Response evaluated by CGI-I

(1) Definition of a formula or derivation

- Response if CGI-I at each time point is 1 or 2

(2) Assessment time

- Week 1, 2, 4, 6, and 8

(3) Imputation method

- If imputing missing values, LOCF method will be used (only at Week 8)

7.1.11 CGI-S

(1) Definition of a formula or derivation

- Measured values will be used.

(2) Assessment time

- Baseline, Week 1, 2, 4, 6, and 8

(3) Imputation method

- If imputing missing values, LOCF method will be used (only at Week 8)

7.1.12 Change in CGI-S from baseline

(1) Definition of a formula or derivation

- CGI-S at each time point – CGI-S (Baseline)

(2) Assessment time

- Week 1, 2, 4, 6, and 8

(3) Imputation method

- If imputing missing values, LOCF method will be used (only at Week 8)

7.1.13 Total $QIDS_{16}$-SR-J score

(1) Definition of a formula or derivation

- Sum of the following nine values
  - Maximum value of sleep items (item 1-4)

- Maximum value of appetite/weight items (item 6-9)
- Maximum value of items related to psychomotor status (item 15 and 16)
- Values for each of the 6 items (item 5 and 10-14) other than the above

(2) Assessment time
- Baseline, Week 1, 2, 4, 6, and 8

(3) Imputation method
- If imputing missing values, LOCF method will be used (only at Week 8)

7.1.14 Change in total $QIDS_{16}$-SR-J score from baseline

(1) Definition of a formula or derivation
- Total $QIDS_{16}$-SR-J score at each time point - total $QIDS_{16}$-SR-J score (Baseline)

(2) Assessment time
- Week 1, 2, 4, 6, and 8

(3) Imputation method
- If imputing missing values, LOCF method will be used (only at Week 8)

7.1.15 Total SDS score

(1) Definition of a formula or derivation
- Sum of SDS 3 items
- If “I have not worked/studied at all during the past week for reasons unrelated to the disorder” is selected, total SDS score will be handled as a missing value

(2) Assessment time
- Baseline, Week 4 and 8

(3) Imputation method
- If imputing missing values, LOCF method will be used (only at Week 8)

7.1.16 Change in total SDS score from baseline

(1) Definition of a formula or derivation
- Total SDS score at each time point - total SDS score (Baseline)

(2) Assessment time
- Week 4 and 8

(3) Imputation method
- If imputing missing values, LOCF method will be used (only at Week 8)

7.1.17 SDS subscale

(1) Definition of a formula or derivation

- Each of SDS 3 items will be used
  - WORK/SCHOOL
  - SOCIAL LIFE
  - FAMILY LIFE/HOME RESPONSIBILITIES

(2) Assessment time
- Baseline, Week 4 and 8

(3) Imputation method
- If imputing missing values, LOCF method will be used (only at Week 8)

7.1.18 Change in SDS subscale from baseline

(1) Definition of a formula or derivation
- SDS subscale at each time point - SDS subscale (Baseline)

(2) Assessment time
- Week 4 and 8

(3) Imputation method
- If imputing missing values, LOCF method will be used (only at Week 8)

7.2 Withdrawal

7.2.1 Number of Days to Withdrawal of Administration (days)

(1) Definition of a formula or derivation
- Date of withdrawal (date on which withdrawal is determined) - Date of the first dose of the investigational drug in the treatment period + 1

7.2.2 Timing of withdrawal of treatment

(1) Definition of a formula or derivation
- In subjects who discontinued the treatment period, 7.2.1 is divided as follows
  - Day 1-7, Day 8-14, Day 15-28, Day 29-42, Day 43-56, Day 57 or more, Not administered

7.3 Adverse events

7.3.1 Adverse Events Resulting in Death

(1) Definition of formula or calculation
- Adverse Events for which "fatal" was selected in outcome

7.3.2 SAEs Excluding Death

(1) Definition of formula or calculation

- SAEs other than those resulting in death

7.3.3 Adverse Events Resulting in Treatment Withdrawal

(1) Definition of formula or calculation

- Adverse events for which “discontinued (no re-treatment)" was selected in action with the study drug.

7.3.4 Adverse Events Resulting in Treatment Interrupted

(1) Definition of formula or calculation

- Adverse events for which “interrupted (temporal suspension)"was selected in action with the study drug.

7.3.5 Common Adverse Events

(1) Definition of a formula or derivation

- Adverse events (PT) that occurred in 5% or more of either treatment group during the aggregation period*

  * See 14.3.1.7.

7.3.6 AEs of Interest

(1) Definition of a formula or derivation

- Adverse events (PT) identified as "AEs of Interest" according to “4.1.2 Contents of the Analysis Data Set (6)”

  ※ The following event groups are defined as "AEs of Interest"

  - Suicide-related adverse events
  - Cardiovascular adverse events

7.3.7 Number of Days to Adverse Event Onset (days)

(1) Definition of formula or calculation

- Adverse events that occurred prior to the date of the first dose of the investigational drug in the treatment period
  - Date of onset - date of the first dose of the investigational drug in treatment period
- Adverse events that occurred on or after the date of the first dose of the investigational drug in the treatment period

- Date of onset - date of the first dose of the investigational drug in the treatment period + 1

7.3.8 Time of onset of the AE

(1) Definition of a formula or derivation

- Adverse events occurring during treatment period: "7.3.7 Number of Days to Adverse Event Onset (days)" are divided as follows
  - Day 1-7, Day 8-14, Day 15-28, Day 29-42, Day 43-56, Day 57 or more
- Adverse events occurring during the follow-up period: The Number of Days from the date of the first dose of the investigational drug in the follow-up period to adverse event onset * is divided as follows
  - Day 1-7, Day 8 or more

*: Calculated as "Date of onset - date of the first dose of the investigational drug in the follow-up period + 1". The date of the first dose of the investigational drug in the follow-up period will be the next day of the last dose of the investigational drug in the treatment period

7.3.9 Duration of adverse events (days)

(1) Definition of a formula or derivation

- Date of resolution or date of confirmation of outcome – date of onset of adverse event + 1

7.3.10 Outcome of Adverse Events

(1) Definition of a formula or derivation

- Resolved: if outcome of the adverse event is " recovered/resolved"
- Unresolved: if outcome of the adverse event is either "recovering/resolving “, "not recovered/not resolved “, "recovered/resolved with sequelae “, or "fatal."

7.4 General laboratory tests

Data will be handled as follows.

- Missing data are not imputed in principle
- Abnormalities obtained from general laboratory tests will be excluded from the analysis. In the individual data list, however, the relevant data will be used with a note of “Abnormal specimen.”
- If the value is greater than or equal to the upper limit of quantitation, or less than the lower limit of quantitation, the limits are used as a measured value in the aggregation

7.4.1 Laboratory Measurements

(1) Definition of a formula or derivation

- Measured values will be used

(2) Assessment time

- Start of screening period, Week 2, 4, 8, and EOT

7.4.2 Change in laboratory values

(1) Definition of a formula or derivation

- Value at each time point - Value at the start of screening period

(2) Assessment time

- Week 2, 4, 8, and EOT

7.4.3 Clinical test value abnormality

(1) Definition of a formula or derivation

The following categories will be used, depending on the relationship between the measured value and the corresponding reference value.

- Within the reference range

  Lower reference value ≤ Measured value ≤ Upper reference value

- Greater than the upper limit of the reference value

  Upper reference value < Measured value

- Less than the lower limit of the reference value

  Measured value < Lower reference values

7.5 Vital signs and body weight

7.5.1 Vital signs and body weight

(1) Definition of a formula or derivation

- Measured values will be used.

(2) Assessment time

- Baseline, Week 1, 2, 4, 6, 8, EOT, and Follow-up Week 1

7.5.2 Changes in vital signs and body weight

(1) Definition of a formula or derivation

- Value at each time point - Value (Baseline)

(2) Assessment time

- Week 1, 2, 4, 6, 8, EOT, and Follow-up Week 1

7.6 ECG

7.6.1 12-lead ECG abnormal

(1) Definition of a formula or derivation

- When "Yes" is selected for the presence or absence of abnormal findings.

(2) Assessment time

- Baseline and EOT

7.7 C-SSRS

7.7.1 C-SSRS

(1) Definition of a formula or derivation

- Definition of a formula or derivation
  - Suicidal ideation

    When "Yes" is selected for any item
    - 1: Wish to be Dead
    - 2: Non-Specific Active Suicidal Thoughts
    - 3: Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
    - 4: Active Suicidal Ideation with Some Intent to Act, without Specific Plan
    - 5: Active Suicidal Ideation with Specific Plan and Intent
  - Suicidal behavior

    When "Yes" is selected for any item
    - Actual Attempt
    - Interrupted Attempt
    - Aborted Attempt or Self-Interrupted Attempt
    - Preparatory Acts or Behavior
    - Suicide
  - Suicidal ideation or behavior
    - When either suicidal ideation or suicidal behavior is "yes"

7.8 Pharmacokinetics

7.8.1 Plasma desvenlafaxine concentration (ng/mL)

Data will be handled as follows.

- Missing data are not imputed in principle
- If the value is no quantitative, it its handled as missing in aggregation

- If the value is below the lower limit of quantitation, it is handled as 0 in aggregation. The value will be shown as *BLQ* in the listing of concentration and the lower limit of quantitation will be shown in a footnote.

(1) Definition of a formula or derivation

- Measured values will be used (*Placebo group is excluded.).

(2) Assessment time

- Week 2, 4, and 8, and EOT

8 Primary analysis

8.1 Efficacy

8.1.1 Definitions of Primary Endpoint

Change in total MADRS score from baseline to Week 8

8.1.2 Primary analysis on primary endpoint

A Mixed-effects Model for Repeated Measures (MMRM) will be used for the main analysis of the primary efficacy endpoint. The analytical model will use a change in total MADRS score from baseline to each assessment timepoint as a response variable; the treatment group, assessment timepoint, and the interaction between the treatment group and assessment timepoint as fixed effects, and the total MADRS score at the baseline as a covariate the structure of error variance as Unstructured, and Kenward Roger as degrees of freedom adjustment. Based on this analytical model, changes in total MADRS score from the baseline to Week 8 visit during treatment period in the MD-120 50 mg and 100 mg groups will be compared to that in the placebo group. For missing data on the response variable, no data will be substituted.

Adjustment of multiplicity will be performed in the main analysis on the efficacy primary endpoint according to a closed testing procedure. Results on the efficacy primary endpoint will be firstly compared between the placebo group and MD-120 50 mg group with a significance level of 5%. Only when Hypothesis 1 is verified, a comparison between the placebo group and MD-120 100 mg group will be made with significance level of 5%.

[Hypothesis 1] Superiority of the MD-120 50 mg group to the placebo group

[Hypothesis 2] Superiority of the MD-120 100 mg group to the placebo group

For more information on the statistics to be calculated, see “14.2.1.1.1 MMRM Analysis of Change in total MADRS score from baseline”. See Appendix 2 for a sample SAS program.

8.1.3 Secondary Analysis on primary endpoint

An analysis of covariance will be performed on the primary endpoint by comparing relevant results in the MD-120 50 mg group and 100 mg group to that in the placebo group. The analytical model will use a change in total MADRS score from baseline to Week 8 visit during treatment period as a response variable; the treatment group as a fixed effect, and the total MADRS score at the baseline as a covariate. For missing data on the response variable, data will be substituted in a last observation carried forward (LOCF) manner.

For more information on the statistics to be calculated, see “14.2.1.1.6 ANCOVA Analysis of Change in total MADRS score from baseline”.

8.1.4 Sensitivity analysis of the primary analysis

The following analysis is performed as a sensitivity analysis for the primary analysis.

8.1.4.1. Tipping Point Analysis of Change in total MADRS score from baseline

The use of MMRM for the primary efficacy analysis is based on the MAR assumption. As a sensitivity analysis for the missing mechanism assumption, Tipping Point Analysis which is based on the MNAR assumptions is performed. The procedure is as follows.

1. Non-monotone missing values of change in total MADRS score are imputed using multiple imputation MCMC method by each treatment group. The number of imputations will be 10, and the random seed will be set to 2970.
2. Monotone missing values of change in total MADRS score in the 10 dataset created in step 1 are imputed using multiple substitution regression method. After imputation, the sensitivity parameter Δ is added to the imputed value. The number of imputations will be 1, and the seed will be set to 8229.
3. The 10 pseudo-complete data generated in step 2 will be compared between MD-120 group and placebo group using the same model as the primary analysis.
4. The 10 obtained analysis results are combined.

The sensitivity parameter Δ is incremented by 1 from 0 to 5.

For more information on the statistics to be calculated, see “14.2.1.1.2 Tipping Point Analysis of Change in total MADRS score from baseline”. See Appendix 2 for a sample SAS program.

8.2 Safety

8.2.1 Definitions of Primary Endpoint

Adverse events during the treatment and follow-up periods

8.2.2 Analysis on primary endpoint

An incidence of adverse events during treatment and follow-up periods in each dose group will be calculated.

8.3 Interim analysis

Not implemented.

8.4 Multiple Comparison / Multiplicity

See 8.1.2

9 General Considerations Regarding the Details of the Planned Analyses

9.1 Definitions of Notations in Planned Analyses

9.1.1 Definitions of Figure and Table Titles

For the planned analyses described from Chapter 10, only the Figure and Table titles are presented as a rule. The titles is defined by the following rule.

- **Rule:** *Analysis method* of *Tabulated variable* (*subgroup*) (*category of tabulation other than subgroup*) (*assessment time point*) (*data imputation method*) (*data set analyzed*)
- **Example:** Descriptive statistics of Systolic Blood Pressure (age) (Week 8) (LOCF) (FAS)

This indicates the calculation of the descriptive statistics for systolic blood pressure at Week 8, with missing data imputed by LOCF, for each age category (e.g., age < 60 years, age ≥ 60 years) in the FAS.

Details of the above rules are as follows.

(1) Identification of analysis method

Unless otherwise specified, the analysis will be performed as described below. Supplemental information about the details of the analysis will be provided separately after the title.

Analysis method displayed in the title	The analysis that will be performed.
Descriptive statistics	Descriptive statistics will be calculated for each treatment group. Descriptive statistics include, unless otherwise specified, the number of subjects, mean, standard deviation, minimum, median, and maximum.
Summary	The number of subjects (N) in the data set analyzed, and the number of subjects (n) and the proportion of subjects will be calculated for each treatment group. Subjects for which the dependent variable for aggregation is missing and are not imputed will not be included in the analysis, and will therefore not be included in the denominator of the ratio calculation.
Summary (adverse events)	The number of subjects (N) in the data set analyzed, the number of subjects with the events (n) and the incidence rates of the events will be calculated for each treatment group. When summarizing by event, in principle, the summary on entire events

Analysis method displayed in the title	The analysis that will be performed.
	will be performed similarly. When data after exposure to the study drug are included, adverse drug reactions should be tabulated similarly as a rule. For events specific to each gender, the number of subjects of that gender will be used for the denominator of the rate.
Profiles	Plot graphs using appropriate statistics, such as the mean value, for each treatment group.
Shift table	A contingency table comparing the results at the baseline with the results at each assessment time point will be prepared for each treatment group.
Disposition	The number of subjects will be calculated for each treatment group.
Distribution	For continuous variables, descriptive statistics will be calculated for each treatment group. Unless otherwise stated, descriptive statistics include the number of subjects (N) in the data set analyzed, mean, standard deviation, minimum, median, and maximum. For discrete variables (including qualitative variables), the number of subjects (N) in the data set analyzed , the number of subjects (n), and the proportion will be calculated for each treatment group. For subjects with missing variables are included in the analysis and also in the denominator of the ratio calculation.
Listings	Listings will be prepared.
Other	The analyses corresponding to the titles will be performed. The details will be described in the SAP to the extent that the analysis can be performed.

(2) Specification of *subgroups*

- See Appendix 1 for the factors used in subgroup analyses.
- If not specified, the analysis is performed without considering the subgroup.

(3) Specification of *tabulation categories other than subgroups*

- The categories are specified in detail (e.g., severity, time of onset).

(4) Specification of *Assessment time*

- The assessment time defined in Chapter 7 corresponding to the *Tabulated variable* is specified.
- When the assessment time is not specified, all of the assessment time defined in Chapter 7 corresponding to the *Tabulated variable* will be used for analyses.

(5) Specification of the *data imputation method*

- The data imputation method is specified when multiple imputation methods are defined in Chapter 7.
- When no data imputation method is specified, data will be replaced according to the data imputation method defined in Chapter 7.Endpoint (dependent variable) Definitions

(6) Specification of the *data set analyzed*

- The data set analyzed is specified

9.1.2 Statistical Tests and Calculations of CI in Figures and Tables

The tests and calculations of CIs will be described separately, after the title. Unless otherwise specified, statistical tests and calculations of CIs will not be performed.

9.1.3 Details of Exploratory Statistical Tests

The details of statistical tests are as follows.

9.1.3.1. Efficacy

Defined in each figure and table

9.1.3.2. Adverse events

(1) Fisher's exact test

The following tests will be performed.

- Test of contingency table for adverse events and treatment groups (2 levels: MD-120 50 mg group and Placebo group)
- Test of contingency table for adverse events and treatment groups (2 levels: MD-120 100 mg group and Placebo group)
- Test of contingency table for adverse events and treatment groups (2 levels: MD-120 50 mg group and MD-120 100 mg group)

9.1.3.3. Clinical Laboratory Values

Changes from baseline will be calculated in accordance with Section 7.4.2 and statistical tests will be performed. For qualitative values, the measured values will be converted into integers and done in the same way as quantitative values.

(1) Wilcoxon 2 sample test

The following tests will be performed.

- Tests comparing changes between MD-120 50 mg group and Placebo group for each assessment time point and for each laboratory parameter
- Tests comparing changes between MD-120 100 mg group and Placebo group for each assessment time point and for each laboratory parameter
- Tests comparing changes between MD-120 50 mg group and MD-120 100 mg group for each assessment time point and for each laboratory parameter

9.1.3.4. Vital signs and weight

(1) Wilcoxon 2 sample test

The following tests will be performed.

- Tests comparing changes between MD-120 50 mg group and Placebo group for each assessment time point and for each parameter
- Tests comparing changes between MD-120 100 mg group and Placebo group for each assessment time point and for each parameter
- Tests comparing changes between MD-120 50 mg group and MD-120 100 mg group for each assessment time point and for each parameter

9.1.3.5. ECG

(1) Fisher's exact test

The following tests will be performed.

- Tests in contingency tables for the presence or absence of abnormal ECG findings and treatment groups
  (2 levels: MD-120 50 mg group and Placebo group)
- Tests in contingency tables for the presence or absence of abnormal ECG findings and treatment groups
  (2 levels: MD-120 100 mg group and Placebo group)
- Tests in contingency tables for the presence or absence of abnormal ECG findings and treatment groups
  (2 levels: MD-120 50 mg group and MD-120 100 mg group

9.2 Supplementary Matters Concerning How to Impute Missing Values

9.2.1 LOCF method

If the value at each time point shown in Section 7.1 is missing, the closest value prior to the planned day of the evaluation will be used for the LOCF imputation. The value used to LOCF imputation will include all data that meet the data adoption conditions from the date of the first dose of the investigational drug in the treatment period (including the same day), regardless of whether or not they are included in the data adoption period.

At the start of the screening period and at baseline, no LOCF imputation will be performed.

The data adoption period and data adoption conditions including the planned day for each time point will be specified in the Handling Plan.

9.3 Rounding of Digits in Analysis

- In principle, rounding will not be performed at all during calculation processes.
- When a nonparametric test based on ranks is performed, the test will be performed after rounding off the variables to 10 decimal places immediately before performing the test.

9.4 Software Used for Analysis

SAS Release 9.4 or later

9.5 Other Precautions

- From Chapter 10 of this SAP, and for chapter numbers for the results of the analyses to be prepared, see the “Structure and Content of Clinical Study Reports”
- This SAP will be reviewed after the database is locked and before unblinding, and the appropriateness of the analysis method in the SAP and the necessity for each analysis are assessed.

9.6 Relevant Publications, Guidelines

Statistical Principles for Clinical Studies Iyakushin No. 1047 (November 30, 1998)

Guidance No. 494 for Investigation of Dose-Response Relationships Needed for Approval of New Drugs (July 25, 1994)

Selection of Control Groups in Clinical Trials and Related Problems Iyakushin Notification No. 136 (February 27, 2001)

Guideline on the Structure and Content of the Study General Report No. 335 (May 1, 1996)

Yutaka Matsuyama, "Analysis of Missing Data in Longitudinal Studies: A Review", Jpn J Biomet, vol. 25, no. 2, pp. 89-116, 2004

Xu Yan, Shiowjen Lee, and Ning Lee, "Missing Data Handling Methods in Medical Device Clinical Trials", Journal of biopharmaceutical statistics, vol. 19, pp. 1085-98, 2009

10 Study Subjects

See chapter 14.

11 Efficacy Evaluation

See chapter 14.

12 Safety Evaluation

See chapter 14.

13 Discussion and Overall Conclusions

Not applicable to the SAP

14 Analysis Figures and Tables

14.1 Disposition of Subjects and Distributions of Prognostic Factors

14.1.1 Disposition of Subjects

14.1.1.1. Disposition of Subjects

Table 14.1.1.1.1 Disposition of Subjects in the Study (1st enrolled subjects)

- Classification is as follows. Aggregation by reason for discontinuation is also performed
  - 1st enrolled, 2nd enrolled, started run-in period, randomized, started treatment period, completed treatment period*, and completed follow-up period†

    *: Subjects who completed without discontinuing the treatment period

    †: Subjects who completed without discontinuing the follow-up period
  - Discontinued screening period, discontinued run-in period, discontinued treatment period, and discontinued follow-up period (Before Week 1 visit, After Week 1 visit)

Table 14.1.1.1.2 Summary of Discontinuation of Treatment Period by timing of occurrence (subjects who discontinued treatment period)

- Summarize discontinuation in the treatment period based on 7.2.2 Timing of withdrawal of treatment. Aggregation by reason for discontinuation is also performed.

14.1.1.2. Protocol Deviation

Table 14.1.1.2.1 Summary of Significant Deviations by Category (1st enrolled subjects)

- The numbers of subjects and the numbers of deviations will be calculated.
- The following categories will be used.

  (1) When the subject is enrolled in the study despite violations of GCP or failure to satisfy inclusion criteria

  (2) When the subject meets the criteria for discontinuation during the study but is not discontinued

  (3) When then subject violates the rules about dose (administration regulations)

(4) When the subject uses prohibited concomitant therapies
(5) When the subject does not receive observations, examinations, and assessment about primary endpoints
(6) When any other important problems occur

14.1.1.3. Structure of Efficacy Analysis Populations

Table 14.1.1.3.1 Structure of Efficacy Analysis Populations (randomized subjects)

- The following categories will be used.
  - Randomized subjects
  - FAS, subjects excluded from the FAS
  - PPS, subjects excluded from the PPS

Table 14.1.1.3.2 Subjects Excluded from Efficacy Analysis Populations (randomized subjects)

- Only the number of subjects will be calculated
- The following categories will be used.
  - Subjects excluded from the FAS
    (1) No investigational drug was administered during the treatment period.
    (2) No baseline or post-treatment value of total MADRS score
  - Subjects excluded from the PPS
    (1) Did not meet the inclusion or exclusion criteria
    (2) Violated protocol “7.1.1 Prohibited concomitant drugs“ or “7.1.2 Prohibited concomitant therapies“ from the start of screening period to the end of treatment period
    (3) used hypnotic/sedative drugs in violation of provisions in protocol “7.1.3 Allowed concomitant drugs“ from the start of screening period to the end of treatment period
    (4) Duration of exposure of the investigational drug was less than 42 days or compliance rate was less than 75% in the treatment period

14.1.1.4. Structure of Safety Analysis Populations

Table 14.1.1.4.1 Structure of Safety Analysis Population (2nd enrolled subjects)

- Classification is as follows
  - 2nd enrolled subjects

- SAF in the run-in period, subjects excluded from SAF in the run-in period
- Randomized subjects
- SAF, subjects excluded from SAF
- SAF in the follow-up period, subjects excluded from SAF in the follow-up period

14.1.1.5. Structure of Pharmacokinetic Analysis Population

Table 14.1.1.5.1 Structure of Pharmacokinetic Analysis Population (randomized subjects)

- Classification is as follows
  - Example of assignment registration
  - Pharmacokinetic analysis set, subjects excluded from Pharmacokinetic analysis set

※ Placebo group is excluded from the tabulation.

14.1.2 Demographic and Other Baseline Characteristics

14.1.2.1. Demographic and Other Baseline Characteristics (Demographic Variables)

Table 14.1.2.1.1 Demographic and Other Baseline Characteristics (Demographic Variables) (FAS)

Table 14.1.2.1.2 Demographic and Other Baseline Characteristics (Demographic Variables) (PPS)

Table 14.1.2.1.3 Demographic and Other Baseline Characteristics (Demographic Variables) (SAF)

14.1.2.2. Demographic and Other Baseline Characteristics (Other Factors)

Table 14.1.2.2.1 Demographic and Other Baseline Characteristics (Other Factors) (FAS)

Table 14.1.2.2.2 Demographic and Other Baseline Characteristics (Other Factors) (PPS)

Table 14.1.2.2.3 Demographic and Other Baseline Characteristics (Other Factors) (SAF)

14.1.2.3. Demographic and Other Baseline Characteristics (Baseline)

Table 14.1.2.3.1 Demographic and Other Baseline Characteristics (Baseline) (FAS)

Table 14.1.2.3.2 Demographic and Other Baseline Characteristics (Baseline) (PPS)

Table 14.1.2.3.3 Demographic and Other Baseline Characteristics (Baseline) (SAF)

14.1.3 Extent of Exposure to Study Drugs

14.1.3.1. Extent of Exposure to Study Drugs

Table 14.1.3.1.1 Extent of Exposure to Study Drugs (FAS)

Table 14.1.3.1.2 Extent of Exposure to Study Drugs (PPS)

Table 14.1.3.1.3 Extent of Exposure to Study Drugs (SAF)

14.2 Efficacy

14.2.1 Total MADRS score

14.2.1.1. Analysis of total MADRS score

14.2.1.1.1. MMRM Analysis of Change in total MADRS score from baseline

The following analyses are performed.

- Model description
  - Response variable: Change in total MADRS score from baseline
  - Fixed effect: treatment group, time point, interaction between treatment group and time point
  - Covariate(s): Total MADRS score (baseline)
  - Covariance Structure: Unstructured
  - Approximation for the degrees of freedom: Kenward Roger
  - Time point included in the analysis: Week 1, 2, 4, 6, and 8
- The following statistics will be calculated:
  - Adjusted mean (for each treatment group)
  - Adjusted mean difference from placebo and its two-sided 95% CI
  - Test for Fixed effect (for each treatment group): p-value
- Comparison
  - MD-120 50 mg group vs Placebo group
  - MD-120 100 mg group vs Placebo group

※ Data from the three groups will be used to estimate differences between groups at each time point using a contrast factor.

※ Analysis using the response variable as Total MADRS score will be performed in the same way.

Table 14.2.1.1.1.1 MMRM Analysis of Change in total MADRS score from baseline (OC) (FAS)

Table 14.2.1.1.1.2 MMRM Analysis of Change in total MADRS score from baseline (OC) (PPS)

14.2.1.1.2. Tipping Point Analysis of Change in total MADRS score from baseline

The model and the statistics to be calculated are the same as in 14.2.1.1.1

Table 14.2.1.1.2.1 Tipping Point Analysis of Change in total MADRS score from baseline (OC) (Week 8) (FAS)

14.2.1.1.3. MMRM Analysis of Change in total MADRS score from baseline (Stratified Analysis)

For the model used in 14.2.1.1.1, one background factor is added and the same analysis is performed

Table 14.2.1.1.3.1 MMRM Analysis of Change in total MADRS score from baseline (Week 8) (Stratification: Demographic variables) (OC) (FAS)

Table 14.2.1.1.3.2 MMRM Analysis of Change in total MADRS score from baseline (Week 8) (Stratification: Other factors) (OC) (FAS)

14.2.1.1.4. MMRM Analysis of Change in total MADRS score from baseline (Subgroup Analysis)

The model and the statistics to be calculated are the same as in 14.2.1.1.1

※ If fewer than 10 subjects are in any of the subgroups, no analysis will be performed in that subgroup.

Table 14.2.1.1.4.1 MMRM Analysis of Change in total MADRS score from baseline (Week 8) (Subgroup: Demographic variables) (OC) (FAS)

Table 14.2.1.1.4.2 MMRM Analysis of Change in total MADRS score from baseline (Week 8) (Subgroup: Other factors) (OC) (FAS)

Table 14.2.1.1.4.3 MMRM Analysis of Change in total MADRS score from baseline (Week 8) (Subgroup: Baseline) (OC) (FAS)

14.2.1.1.5. MMRM(Overall) Analysis of Change in total MADRS score from baseline

The following analyses are performed.

- Model description
  - Response variable: Change in total MADRS score from baseline
  - Fixed effect: treatment group, time point
  - Covariate(s): Total MADRS score (baseline)
  - Covariance Structure: Unstructured
  - Approximation for the degrees of freedom: Kenward Roger
  - Time point included in the analysis: Week 1, 2, 4, 6, and 8
- The following statistics will be calculated:
  - Adjusted mean (for each treatment group)
  - Adjusted mean difference from placebo and its two-sided 95% CI

- Test for Fixed effect (for each treatment group): p-value

- Comparison
  - MD-120 50 mg group vs Placebo group
  - MD-120 100 mg group vs Placebo group

    ※ Data from the three groups will be used to estimate differences between groups across the overall treatment period using a contrast factor.

Table 14.2.1.1.5.1 MMRM(Overall) Analysis of Change in total MADRS score from baseline (OC) (FAS)

14.2.1.1.6. ANCOVA Analysis of Change in total MADRS score from baseline

The following analyses will be performed.

- Model description
  - Dependent variable: Change in total MADRS score from baseline
  - Fixed effect: treatment group
  - Covariate(s): Total MADRS score (baseline)
- The following statistics will be calculated:
  - Adjusted mean (for each treatment group)
  - Adjusted mean difference from placebo and its two-sided 95% CI
  - Test for Fixed effect (for each treatment group): p-value
- Comparison
  - MD-120 50 mg group vs Placebo group
  - MD-120 100 mg group vs Placebo group

    ※ Data from the three groups will be used to estimate differences between groups at each time point using a contrast factor.

※ Analysis using the response variable as Total MADRS score will be performed in the same way.

Table 14.2.1.1.6.1 ANCOVA Analysis of Change in total MADRS score from baseline (LOCF) (FAS)

Table 14.2.1.1.6.2 ANCOVA Analysis of Change in total MADRS score from baseline (OC) (FAS)

Table 14.2.1.1.6.3 ANCOVA Analysis of Change in total MADRS score from baseline (LOCF) (PPS)

Table 14.2.1.1.6.4 ANCOVA Analysis of Change in total MADRS score from baseline (OC) (PPS)

14.2.1.1.7. ANCOVA Analysis of Change in total MADRS score from baseline (Subgroup Analysis)

The model and the statistics to be calculated are the same as in 14.2.1.1.1

※ If fewer than 10 subjects are in any of the subgroups, no analysis will be performed in that subgroup.

Table 14.2.1.1.7.1 ANCOVA Analysis of Change in total MADRS score from baseline (Week 8) (Subgroup: Demographic variables) (LOCF) (FAS)

Table 14.2.1.1.7.2 ANCOVA Analysis of Change in total MADRS score from baseline (Week 8) (Subgroup: Other factors) (LOCF) (FAS)

Table 14.2.1.1.7.3 ANCOVA Analysis of Change in total MADRS score from baseline (Week 8) (Subgroup: Baseline) (LOCF) (FAS)

14.2.1.2. Description of total MADRS score

14.2.1.2.1. Descriptive Statistics of total MADRS score and Change in total MADRS score from baseline

- The following statistics will be calculated:
  - Mean and its two-sided 95% CI

Table 14.2.1.2.1.1 Descriptive Statistics of total MADRS score and Change in total MADRS score from baseline (LOCF) (FAS)

Table 14.2.1.2.1.2 Descriptive Statistics of total MADRS score and Change in total MADRS score from baseline (OC) (FAS)

Table 14.2.1.2.1.3 Descriptive Statistics of total MADRS score and Change in total MADRS score from baseline (LOCF) (PPS)

Table 14.2.1.2.1.4 Descriptive Statistics of total MADRS score and Change in total MADRS score from baseline (OC) (PPS)

14.2.1.2.2. Descriptive Statistics of total MADRS score and Change in total MADRS score from baseline (Subgroup Analysis)

- The following statistics will be calculated:
  - Mean and its two-sided 95% CI

Table 14.2.1.2.2.1 Descriptive Statistics of total MADRS score and Change in total MADRS score from baseline (Subgroup: Demographic variables) (Week 8) (LOCF) (FAS)

Table 14.2.1.2.2.2 Descriptive Statistics of total MADRS score and Change in total MADRS score from baseline (Subgroup: Other factors) (Week 8) (LOCF) (FAS)

Table 14.2.1.2.2.3 Descriptive Statistics of total MADRS score and Change in total MADRS score from baseline (Subgroup: Baseline) (Week 8) (LOCF) (FAS)

Table 14.2.1.2.2.4 Descriptive Statistics of total MADRS score and Change in total MADRS score from baseline (Subgroup: Study Center) (Week 8) (LOCF) (FAS)

14.2.1.3. Graphs of total MADRS score

14.2.1.3.1. Profiles of total MADRS score and Change in total MADRS score from baseline (MMRM Analysis)

See 14.2.1.1.1

Figure 14.2.1.3.1.1 Profiles of total MADRS score and Change in total MADRS score from baseline (MMRM Analysis) (OC) (FAS)

14.2.1.3.2. Profiles of total MADRS score and Change in total MADRS score from baseline (ANCOVA Analysis)

See 14.2.1.1.6

Figure 14.2.1.3.2.1 Profiles of total MADRS score and Change in total MADRS score from baseline (ANCOVA Analysis) (OC/LOCF at Week 8) (FAS)

14.2.2 Response evaluated by total MADRS score

14.2.2.1. Analysis of response evaluated by total MADRS score

14.2.2.1.1. GEE analysis of response evaluated by total MADRS score

The following analyses are performed.

- Model description
  - Response variable: Response evaluated by total MADRS score (Link Function: logit)
  - Fixed effect: treatment group, time point, interaction between treatment group and time point
  - Covariate(s): Total MADRS score (baseline)
  - Covariance Structure: Unstructured
  - Time point included in the analysis: Week 1, 2, 4, 6, and 8
- The following statistics will be calculated:
  - Odds ratio and its two-sided 95% CI versus placebo group
  - Test for Fixed effect (for each treatment group): p-value
    ※If at least one of the two groups being compared has no response cases, these statistics are not calculated.

- Comparison
  - MD-120 50 mg group and Placebo group
  - MD-120 100 mg group and Placebo group

    ※Data from the three groups will be used to estimate differences between groups at each time point.

Table 14.2.2.1.1.1 GEE analysis of response evaluated by total MADRS score (OC) (FAS)

14.2.2.1.2. Logistic regression of response evaluated by total MADRS score

The following analyses are performed.

- Model description
  - Response variable: response evaluated by total MADRS score
  - Fixed effect: treatment group
  - Covariate(s): Total MADRS score (baseline)
- The following statistics will be calculated:
  - Odds ratio and its two-sided 95% CI versus placebo group
  - Test for Fixed effect (for each treatment group): p-value

    ※If at least one of the two groups being compared has no response cases, these statistics are not calculated.
- Comparison
  - MD-120 50 mg group and Placebo group
  - MD-120 100 mg group and Placebo group

    ※Data from the three groups will be used to estimate differences between groups at each time point.

Table 14.2.2.1.2.1 Logistic regression of response evaluated by total MADRS score (OC/LOCF at Week 8) (FAS)

14.2.2.1.3. Comparison of response evaluated by total MADRS score

The following analyses are performed.

- The following statistics will be calculated:
  - Fisher's Exact Test: p-value
- Comparison
  - MD-120 50 mg group and Placebo group
  - MD-120 100 mg group and Placebo group

Table 14.2.2.1.3.1 Comparison of response evaluated by total MADRS score (OC/LOCF at Week 8) (FAS)

14.2.2.2. Description of response evaluated by total MADRS score

14.2.2.2.1. Aggregation of response evaluated by total MADRS score

Not applicable

14.2.2.3. Graphs of response evaluated by total MADRS score

Not applicable

14.2.3 Remission evaluated by total MADRS score

14.2.3.1. Analysis of remission evaluated by total MADRS score

14.2.3.1.1. GEE analysis of remission evaluated by total MADRS score

The model and the statistics to be calculated will conform to 14.2.2.1.1

Table 14.2.3.1.1.1 GEE analysis of remission evaluated by total MADRS score (OC) (FAS)

14.2.3.1.2. Logistic regression of remission evaluated by total MADRS score

The model and the statistics to be calculated will conform to 14.2.2.1.2

Table 14.2.3.1.2.1 Logistic regression of remission evaluated by total MADRS score (OC/LOCF at Week 8) (FAS)

14.2.3.1.3. Comparison of remission evaluated by total MADRS score

Table 14.2.3.1.3.1 Comparison of remission evaluated by total MADRS score (OC/LOCF at Week 8) (FAS)

14.2.3.2. Description of remission evaluated by total MADRS score

14.2.3.2.1. Aggregation of remission evaluated by total MADRS score

Not applicable

14.2.3.3. Graphs of remission evaluated by total MADRS score

Not applicable

14.2.4 Total HAMD17 score

14.2.4.1. Analysis of total HAMD17 score

14.2.4.1.1. MMRM Analysis of Change in total HAMD17 score from baseline

The model and the statistics to be calculated will conform to 14.2.1.1.1

Table 14.2.4.1.1.1 MMRM Analysis of Change in total HAMD17 score from baseline (OC) (FAS)

Table 14.2.4.1.1.2 MMRM Analysis of Change in total HAMD17 score from baseline (OC) (PPS)

14.2.4.1.2. MMRM Analysis of Change in total HAMD17 score from baseline (Stratified Analysis)

For the model used in 14.2.4.1.1, one background factor is added and the same analysis is performed

Table 14.2.4.1.2.1 MMRM Analysis of Change in total HAMD17 score from baseline (Week 8) (Stratification: Demographic variables) (OC) (FAS)

Table 14.2.4.1.2.2 MMRM Analysis of Change in total HAMD17 score from baseline (Week 8) (Stratification: Other factors) (OC) (FAS)

14.2.4.1.3. MMRM Analysis of Change in total HAMD17 score from baseline (Subgroup Analysis)

The model and the statistics to be calculated are the same as in 14.2.4.1.1

※ If fewer than 10 subjects are in any of the subgroups, no analysis will be performed in that subgroup.

Table 14.2.4.1.3.1 MMRM Analysis of Change in total HAMD17 score from baseline (Week 8) (Subgroup: Demographic variables) (OC) (FAS)

Table 14.2.4.1.3.2 MMRM Analysis of Change in total HAMD17 score from baseline (Week 8) (Subgroup: Other factors) (OC) (FAS)

Table 14.2.4.1.3.3 MMRM Analysis of Change in total HAMD17 score from baseline (Week 8) (Subgroup: Baseline) (OC) (FAS)

14.2.4.1.4. MMRM(Overall) Analysis of Change in total HAMD17 score from baseline

The model and the statistics to be calculated will conform to 14.2.1.1.5

Table 14.2.4.1.4.1 MMRM(Overall) Analysis of Change in total HAMD17 score from baseline (OC) (FAS)

14.2.4.1.5. ANCOVA Analysis of Change in total HAMD17 score from baseline

The model and the statistics to be calculated will conform to 14.2.1.1.6

Table 14.2.4.1.5.1 ANCOVA Analysis of Change in total HAMD17 score from baseline (LOCF) (FAS)

Table 14.2.4.1.5.2 ANCOVA Analysis of Change in total HAMD17 score from baseline (OC) (FAS)
Table 14.2.4.1.5.3 ANCOVA Analysis of Change in total HAMD17 score from baseline (LOCF) (PPS)
Table 14.2.4.1.5.4 ANCOVA Analysis of Change in total HAMD17 score from baseline (OC) (PPS)

14.2.4.1.6. ANCOVA Analysis of Change in total HAMD17 score from baseline (Subgroup Analysis)

The model and the statistics to be calculated are the same as in 14.2.4.1.5
※ If fewer than 10 subjects are in any of the subgroups, no analysis will be performed in that subgroup.

Table 14.2.4.1.6.1 ANCOVA Analysis of Change in total HAMD17 score from baseline (Week 8) (Subgroup: Demographic variables) (LOCF) (FAS)
Table 14.2.4.1.6.2 ANCOVA Analysis of Change in total HAMD17 score from baseline (Week 8) (Subgroup: Other factors) (LOCF) (FAS)
Table 14.2.4.1.6.3 ANCOVA Analysis of Change in total HAMD17 score from baseline (Week 8) (Subgroup: Baseline) (LOCF) (FAS)

14.2.4.2. Description of total HAMD17 score

14.2.4.2.1. Descriptive Statistics of total HAMD17 score and Change in total HAMD17 score from baseline

- Statistics to be calculated
  - Mean and its two-sided 95% CI

Table 14.2.4.2.1.1 Descriptive Statistics of total HAMD17 score and Change in total HAMD17 score from baseline (LOCF) (FAS)
Table 14.2.4.2.1.2 Descriptive Statistics of total HAMD17 score and Change in total HAMD17 score from baseline (OC) (FAS)
Table 14.2.4.2.1.3 Descriptive Statistics of total HAMD17 score and Change in total HAMD17 score from baseline (LOCF) (PPS)
Table 14.2.4.2.1.4 Descriptive Statistics of total HAMD17 score and Change in total HAMD17 score from baseline (OC) (PPS)

14.2.4.2.2. Descriptive Statistics of total HAMD17 score and Change in total HAMD17 score from baseline (Subgroup Analysis)

- Statistics to be calculated

- Mean and its two-sided 95% CI

Table 14.2.4.2.2.1 Descriptive Statistics of total HAMD17 score and Change in total HAMD17 score from baseline (Subgroup: Demographic variables) (Week 8) (LOCF) (FAS)

Table 14.2.4.2.2.2 Descriptive Statistics of total HAMD17 score and Change in total HAMD17 score from baseline (Subgroup: Other factors) (Week 8) (LOCF) (FAS)

Table 14.2.4.2.2.3 Descriptive Statistics of total HAMD17 score and Change in total HAMD17 score from baseline (Subgroup: Baseline) (Week 8) (LOCF) (FAS)

Table 14.2.4.2.2.4 Descriptive Statistics of total HAMD17 score and Change in total HAMD17 score from baseline (Subgroup: Study Center) (Week 8) (LOCF) (FAS)

14.2.4.3. Graphs of total HAMD17 score

14.2.4.3.1. Profiles of total HAMD17 score and Change in total HAMD17 score from baseline (MMRM analysis)

See 14.2.4.1.1

Figure 14.2.4.3.1.1 Profiles of total HAMD17 score and Change in total HAMD17 score from baseline (MMRM analysis) (OC) (FAS)

14.2.4.3.2. Profiles of total HAMD17 score and Change in total HAMD17 score from baseline (ANCOVA Analysis)

See 14.2.4.1.5

Figure 14.2.4.3.2.1 Profiles of total HAMD17 score and Change in total HAMD17 score from baseline (ANCOVA Analysis) (OC/LOCF at Week 8) (FAS)

14.2.4.3.3. Correlation between total HAMD17 score and total MADRS score

- The following statistics will be calculated:
  - Correlation coefficient (Pearson's product moment correlation coefficient)
  - Test of no correlation: p-value

Figure 14.2.4.3.3.1 Correlation between total HAMD17 score and total MADRS score (Week 8) (LOCF) (FAS)

Figure 14.2.4.3.3.2 Correlation between change in total HAMD17 score and change in total MADRS score (Week 8) (LOCF) (FAS)

14.2.5 Response evaluated by total HAMD17 score

14.2.5.1. Analysis of response evaluated by total HAMD17 score

14.2.5.1.1. GEE analysis of response evaluated by total HAMD17 score

The model and the statistics to be calculated will conform to 14.2.2.1.1

Table 14.2.5.1.1.1 GEE analysis of response evaluated by total HAMD17 score (OC) (FAS)

14.2.5.1.2. Logistic regression of response evaluated by total HAMD17 score

The model and the statistics to be calculated will conform to 14.2.2.1.2

Table 14.2.5.1.2.1 Logistic regression of response evaluated by total HAMD17 score (OC/LOCF at Week 8) (FAS)

14.2.5.1.3. Comparison of response evaluated by total HAMD17 score

Table 14.2.5.1.3.1 Comparison of response evaluated by total HAMD17 score (OC/LOCF at Week 8) (FAS)

14.2.5.2. Description of response evaluated by total HAMD17 score

14.2.5.2.1. Aggregation of response evaluated by total HAMD17 score

Not applicable

14.2.5.3. Graphs of remission evaluated by total HAMD17 score

Not applicable

14.2.6 Remission evaluated by total HAMD17 score

14.2.6.1. Analysis of remission evaluated by total HAMD17 score

14.2.6.1.1. GEE analysis of remission evaluated by total HAMD17 score

The model and the statistics to be calculated will conform to 14.2.2.1.1

Table 14.2.6.1.1.1 GEE analysis of remission evaluated by total HAMD17 score (OC) (FAS)

14.2.6.1.2. Logistic regression of remission evaluated by total MADRS score

The model and the statistics to be calculated will conform to 14.2.2.1.2

Table 14.2.6.1.2.1 Logistic regression of remission evaluated by total HAMD17 score (OC/LOCF at Week 8) (FAS)

14.2.6.1.3. Comparison of remission evaluated by total HAMD17 score

Table 14.2.6.1.3.1 Comparison of remission evaluated by total HAMD17 score (OC/LOCF at Week 8) (FAS)

14.2.6.2. Description of remission evaluated by total HAMD17 score

14.2.6.2.1. Aggregation of remission evaluated by total HAMD17 score

Not applicable

14.2.6.3. Graphs of remission evaluated by total HAMD17 score

Not applicable

14.2.7 CGI-I

14.2.7.1. Analysis of CGI-I

14.2.7.1.1. MMRM Analysis of CGI-I

The following analyses are performed.

- Model description
  - Response variable: CGI-I
  - Fixed effect: treatment group, time point, interaction between treatment group and time point
  - Covariance Structure: Unstructured
  - Approximation for the degrees of freedom: Kenward Roger
  - Time point included in the analysis: Week 1, 2, 4, 6, and 8
- The following statistics will be calculated:
  - Adjusted mean (for each treatment group)
  - Adjusted mean difference from placebo and its two-sided 95% CI
  - Test for Fixed effect (for each treatment group): p-value
- Comparison
  - MD-120 50 mg group vs Placebo group
  - MD-120 100 mg group vs Placebo group

    ※ Data from the three groups will be used to estimate differences between groups at each time point using a contrast factor.

Table 14.2.7.1.1.1 MMRM Analysis of CGI-I (OC) (FAS)

14.2.7.1.2. ANOVA Analysis of CGI-I

The following analyses are performed.

- Model description
  - Response variable: CGI-I

- Fixed effect: treatment group
- The following statistics will be calculated:
  - Adjusted mean (for each treatment group)
  - Adjusted mean difference from placebo and its two-sided 95% CI
  - Test for Fixed effect (for each treatment group): p-value
- Comparison
  - MD-120 50 mg group vs Placebo group
  - MD-120 100 mg group vs Placebo group

※ Data from the three groups will be used to estimate differences between groups at each time point using a contrast factor.

Table 14.2.7.1.2.1 ANOVA Analysis of CGI-I (OC/LOCF at Week 8) (FAS)

14.2.7.1.3. CMH test of CGI-I

The following analyses are performed.

- Model
  - Row variable: Treatment group (*Only 2 groups to be compared are used)
  - Column variable: CGI-I
  - Stratification Variables: None
- Comparison
  - MD-120 50 mg group vs Placebo group
  - MD-120 100 mg group vs Placebo group
- The following statistics will be calculated:
  - ANOVA statistic (ridit score): p-value

Table 14.2.7.1.3.1 CMH test of CGI-I (OC/LOCF at Week 8) (FAS)

14.2.7.2. Description of CGI-I

14.2.7.2.1. Descriptive Statistics of CGI-I

- The following statistics will be calculated:
  - Mean and its two-sided 95% CI

Table 14.2.7.2.1.1 Descriptive Statistics of CGI-I (OC/LOCF at Week 8) (FAS)

14.2.7.3. Graphs of CGI-I

14.2.7.3.1. Profiles of CGI-I (MMRM analysis)

- See 14.2.7.1.1

Figure 14.2.7.3.1.1 Profiles of CGI-I (MMRM analysis) (OC) (FAS)

14.2.8 Response evaluated by CGI-I

14.2.8.1. Analysis of response evaluated by CGI-I

14.2.8.1.1. GEE Analysis of response evaluated by CGI-I

The model and the statistics to be calculated are in accordance with 14.2.2.1.1 (* Baseline adjustment will not be performed.)

Table 14.2.8.1.1.1 GEE Analysis of response evaluated by CGI-I (OC) (FAS)

14.2.8.1.2. Logistic regression of response evaluated by CGI-I

The model and the statistics to be calculated are in accordance with 14.2.2.1.2 (* Baseline adjustment will not be performed.)

Table 14.2.8.1.2.1 Logistic regression of response evaluated by CGI-I (OC/LOCF at Week 8) (FAS)

14.2.8.1.3. Comparison of responses in CGI-I

Table 14.2.8.1.3.1 Comparison of responses in CGI-I (OC/LOCF at Week 8) (FAS)

14.2.8.2. Description of response in CGI-I

14.2.8.2.1. Aggregation of response evaluated by CGI-I

Not applicable

14.2.8.3. Graphs of responses in CGI-I

Not applicable

14.2.9 CGI-S

14.2.9.1. Analysis of CGI-S

14.2.9.1.1. MMRM Analysis of Change in CGI-S from baseline

The model and the statistics to be calculated will conform to 14.2.1.1.1

Table 14.2.9.1.1.1 MMRM Analysis of Change in CGI-S from baseline (OC) (FAS)

14.2.9.1.2. ANCOVA Analysis of Change in CGI-S from baseline

The model and the statistics to be calculated will conform to 14.2.1.1.6

Table 14.2.9.1.2.1 ANCOVA Analysis of Change in CGI-S from baseline (OC/LOCF at Week 8) (FAS)

14.2.9.2. Description of CGI-S

14.2.9.2.1. Descriptive Statistics of CGI-S and Change in CGI-S from baseline

- The following statistics will be calculated:
  - Mean and its two-sided 95% CI

Table 14.2.9.2.1.1 Descriptive Statistics of CGI-S and Change in CGI-S from baseline (OC/LOCF at Week 8) (FAS)

14.2.9.2.2. Aggregation of CGI-S

Table 14.2.9.2.2.1 Aggregation of CGI-S (OC/LOCF at Week 8) (FAS)

14.2.9.3. Graphs of CGI-S

14.2.9.3.1. Profiles of CGI-S and Change in CGI-S from baseline (MMRM analysis)

See 14.2.9.1.1

Figure 14.2.9.3.1.1 Profiles of CGI-S and Change in CGI-S from baseline (MMRM Analysis) (OC) (FAS)

14.2.10 Total $QIDS_{16}$-SR-J score

14.2.10.1. Analysis of Total $QIDS_{16}$-SR-J score

14.2.10.1.1. MMRM Analysis of Change in total $QIDS_{16}$-SR-J score from baseline

The model and the statistics to be calculated will conform to 14.2.1.1.1

Table 14.2.10.1.1.1 MMRM Analysis of Change in total $QIDS_{16}$-SR-J score from baseline (OC) (FAS)

14.2.10.1.2. ANCOVA Analysis of Change in total $QIDS_{16}$-SR-J score from baseline

The model and the statistics to be calculated will conform to 14.2.1.1.6

Table 14.2.10.1.2.1 ANCOVA Analysis of Change in total $QIDS_{16}$-SR-J score from baseline (OC/LOCF at Week 8) (FAS)

14.2.10.2. Description of total $QIDS_{16}$-SR-J score

14.2.10.2.1. Descriptive Statistics of total $QIDS_{16}$-SR-J score and Change in total $QIDS_{16}$-SR-J score from baseline

- The following statistics will be calculated:

- Mean and its two-sided 95% CI

Table 14.2.10.2.1.1 Descriptive Statistics of total $QIDS_{16}$-SR-J score and Change in total $QIDS_{16}$-SR-J score from baseline (OC/LOCF at Week 8) (FAS)

14.2.10.3. Graphs of total $QIDS_{16}$-SR-J score

14.2.10.3.1. Profiles of total $QIDS_{16}$-SR-J score and Change in total $QIDS_{16}$-SR-J score from baseline (MMRM analysis)

See 14.2.10.1.1

Figure 14.2.10.3.1.1 Profiles of total $QIDS_{16}$-SR-J score and Change in total $QIDS_{16}$-SR-J score from baseline (MMRM Analysis) (OC) (FAS)

14.2.11 Total SDS score

14.2.11.1. Analysis of Total SDS score

14.2.11.1.1. MMRM Analysis of Change in total SDS score from baseline

The model and the statistics to be calculated will conform to 14.2.1.1.1

Table 14.2.11.1.1.1 MMRM Analysis of Change in total SDS score from baseline (OC) (FAS)

Table 14.2.11.1.1.2 MMRM Analysis of Change in SDS (WORK/SCHOOL) from baseline (OC) (FAS)

Table 14.2.11.1.1.3 MMRM Analysis of Change in SDS (SOCIAL LIFE) from baseline (OC) (FAS)

Table 14.2.11.1.1.4 MMRM Analysis of Change in SDS (FAMILY LIFE/HOME RESPONSIBILITIES) from baseline (OC) (FAS)

14.2.11.1.2. ANCOVA Analysis of Change in total SDS score from baseline

The model and the statistics to be calculated will conform to 14.2.1.1.6

Table 14.2.11.1.2.1 ANCOVA Analysis of Change in total SDS score from baseline (OC/LOCF at Week 8) (FAS)

Table 14.2.11.1.2.2 ANCOVA Analysis of Change in SDS (WORK/SCHOOL) from baseline (OC/LOCF at Week 8) (FAS)

Table 14.2.11.1.2.3 ANCOVA Analysis of Change in SDS (SOCIAL LIFE) from baseline (OC/LOCF at Week 8) (FAS)

Table 14.2.11.1.2.4 ANCOVA Analysis of Change in SDS (FAMILY LIFE/HOME RESPONSIBILITIES) from baseline (OC/LOCF at Week 8) (FAS)

14.2.11.2. Description of total SDS score

14.2.11.2.1. Descriptive Statistics of total SDS score and Change in total SDS score from baseline

- The following statistics will be calculated:
  - Mean and its two-sided 95% CI

Table 14.2.11.2.1.1 Descriptive Statistics of total SDS score and Change in total SDS score from baseline (OC/LOCF at Week 8) (FAS)

Table 14.2.11.2.1.2 Descriptive Statistics of SDS subscale and Change in SDS subscale from baseline (OC/LOCF at Week 8) (FAS)

14.2.11.3. Graphs of total SDS score

14.2.11.3.1. Profiles of total SDS score and Change in total SDS score from baseline (MMRM analysis)

See 14.2.11.1.1

Figure 14.2.11.3.1.1 Profiles of total SDS score and Change in total SDS score from baseline (MMRM Analysis) (OC) (FAS)

14.3 Safety

14.3.1 Adverse events

14.3.1.1. Brief Summary of Adverse Events

The number of subjects with the following events and the incidence rate are calculated. Adverse reactions are also summarized.

- Adverse events
- Severe adverse events
- Adverse events leading to death
- Serious adverse events excluding death
- Adverse events leading to treatment withdrawal

Table 14.3.1.1.1 Brief Summary of Adverse Events (Treatment and Follow-up period) (SAF)

Table 14.3.1.1.2 Brief Summary of Adverse Events (Treatment period) (SAF)

Table 14.3.1.1.3 Brief Summary of Adverse Events (Follow-up period) (SAF in the follow-up period)

Table 14.3.1.1.4 Brief Summary of Adverse Events (Run-in period) (SAF in the run-in period)

14.3.1.2. Summary of Adverse Events (Subgroup Analysis)

Table 14.3.1.2.1 Summary of Adverse Events (Subgroup: Demographic Variables) (Treatment and Follow-up period) (SAF)

Table 14.3.1.2.2 Summary of Adverse Events (Subgroup: Other Factors) (Treatment and Follow-up period) (SAF)

Table 14.3.1.2.3 Summary of Adverse Events (Subgroup: Baseline) (Treatment and Follow-up period) (SAF)

14.3.1.3. Summary of Adverse Events by SOC and PT

Table 14.3.1.3.1 Summary of Adverse Events by SOC and PT (Treatment and Follow-up period) (SAF)

- Fisher's exact test

Table 14.3.1.3.2 Summary of Adverse Events by SOC and PT (Treatment period) (SAF)

- Fisher's exact test

Table 14.3.1.3.3 Summary of Adverse Events by SOC and PT (Follow-up period) (SAF in the Follow-up period)

- Fisher's exact test

Table 14.3.1.3.4 Summary of Adverse Events by SOC and PT (Run-in period) (SAF in the run-in period)

14.3.1.4. Summary of Adverse Events by SOC and PT (Subgroup Analysis)

Table 14.3.1.4.1 Summary of Adverse Events by SOC and PT (Subgroup: Sex) (Treatment and Follow-up period) (SAF)

Table 14.3.1.4.2 Summary of Adverse Events by SOC and PT s (Subgroup: Age) (Treatment and Follow-up period) (SAF)

14.3.1.5. Summary of Adverse Events by SOC and PT by severity

Table 14.3.1.5.1 Summary of Adverse Events by SOC and PT by severity (Treatment and Follow-up period) (SAF)

When a single subject experiences multiple episodes of the same event, only the most severe episode will be counted.

14.3.1.6. Summary of Adverse Events by SOC and PT by timing of occurrence

The incidence rate is defined as follows.

- Number of subjects with event/Number of subjects * ×100

  The number of subjects * is defined as follows

  - For each category (day X ≦ Number of Days to Adverse Event Onset (days) ≦ day Y (see "7.3.8 Time of onset of the AE")), only subjects meeting the following conditions are included in the denominator.
    - Number of days to completion of follow-up # ≧ Lower limit (day X) of the number of days to the event included in the summary

      # Number of days to completion of follow-up will be defined as (date of completion of follow-up - date of the first dose of the investigational drug in the treatment period or follow-up period + 1). The date of completion of follow-up will be the latest date of week 1 visit during follow-up period or the time of premature termination, end of follow-up period or the time of premature termination, or existence of the subject. Subjects with missing follow-up will always be included in the denominator. Adverse events for which the time of onset is missing will be excluded from the tabulation.

Table 14.3.1.6.1 Summary of Adverse Events by SOC and PT by timing of occurrence (Treatment and Follow-up period) (SAF)

14.3.1.7. Common Adverse Events

Table 14.3.1.7.1 Summary of Common Adverse Events by PT (Treatment and Follow-up period) (SAF)

- The following statistics will be calculated:
  - Differences in the incidence rates of the events and its two-sided 95% CI
- Comparison
  - MD-120 50 mg group vs Placebo group
  - MD-120 100 mg group vs Placebo group
  - MD-120 100 mg group vs MD-120 50 mg group

Table 14.3.1.7.2 Descriptive Statistics of Number of Days to Onset of Common Adverse Events Treatment and Follow-up period) (SAF)

When a single subject experiences multiple episodes of the same event, only the first occurrence of the event will be used.

Table 14.3.1.7.3 Descriptive Statistics of Duration of Relatively Frequent Adverse Events Treatment and Follow-up period) (SAF)

When a single subject experiences multiple episodes of the same event, only the episode with the longest duration will be counted. Only the recovered/resolved events will be considered.

Table 14.3.1.7.4 Summary of Outcomes of Relatively Frequent Adverse Events Treatment and Follow-up period) (SAF)

When a single subject experiences multiple episodes of the same event, only the unrecovered/unresolved episode will be counted.

Table 14.3.1.7.5 Summary of Common Adverse Events by PT (Follow-up period) (SAF in the follow-up period)

14.3.1.8. AEs of Interest

- The following statistics will be calculated:
  - Differences in the incidence rates of the events and its two-sided 95% CI
- Comparison
  - MD-120 50 mg group vs Placebo group
  - MD-120 100 mg group vs Placebo group
  - MD-120 100 mg group vs MD-120 50 mg group

Table 14.3.1.8.1 Summary of Suicide-related Adverse Events by PT (Treatment and Follow-up period) (SAF)

Table 14.3.1.8.2 Summary of Cardiovascular Adverse Events by PT (Treatment and Follow-up period) (SAF)

14.3.2 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

14.3.2.1. Adverse Events Resulting in Death

Table 14.3.2.1.1 Listing of Adverse Events Resulting in Death

List all adverse events that occurred in subjects who experienced adverse events resulting in death.

14.3.2.2. SAEs Excluding Death

Table 14.3.2.2.1 Listing of SAEs Excluding Death

List all adverse events that occurred in subjects who experienced SAEs excluding death.

Table 14.3.2.2.2 Summary of SAEs Excluding Death by SOC and PT (Treatment and follow-up period) (SAF)

14.3.2.3. Adverse Events Resulting in the treatment Withdrawal

Table 14.3.2.3.1 Listing of Adverse Events Resulting in Treatment Withdrawal

List all adverse events that occurred in subjects who experienced adverse events resulting in treatment withdrawal.

Table 14.3.2.3.2 Summary of Adverse Events Resulting in Treatment Withdrawal by SOC and PT (Treatment period) (SAF)

14.3.2.4. Adverse Events Resulting in Treatment Interrupted

Table 14.3.2.4.1 Listing of Adverse Events Resulting in Treatment Interrupted

List all adverse events that occurred in subjects who experienced adverse events resulting in treatment Interrupted.

Table 14.3.2.4.2 Summary of Adverse Events Resulting in Treatment Interrupted by SOC and PT (Treatment period) (SAF)

14.3.3 Descriptions of Deaths, Other Serious Adverse Events and Other Significant Adverse Events

Not applicable to the SAP

14.3.4 Laboratory Measurements

14.3.4.1. Laboratory Measurements

Table 14.3.4.1.1 Descriptive Statistics of Laboratory Measurement (Quantitative Value) (SAF)

- Wilcoxon 2-sample test

Table 14.3.4.1.2 Shift Table of Laboratory Measurement (Qualitative Value) (SAF)

- Wilcoxon 2-sample test

14.3.4.2. Laboratory Abnormalities

Table 14.3.4.2.1 Shift Table of Laboratory Abnormalities (SAF)

The following variables will be classified and summarized according to "7.4.3 Clinical test value abnormality"

- Row Variable: Measurements at the Start of Screening period
- Column variables: Minimum and maximum values after administration in the treatment period

14.3.4.3. Laboratory box plots

Figure 14.3.4.3.1 Box plots of Laboratory Measurements (SAF)

Only for parameters for which the reference values are the same for both males and females

Figure 14.3.4.3.2 Box plots of Laboratory Measurements (Subgroup: Sex) (SAF)

Only for parameters for which the reference values are different for males and females

14.3.5 Vital Signs and Body Weight

14.3.5.1. Descriptive Statistics of Vital Sign and Body Weight

Table 14.3.5.1.1 Descriptive Statistics of Vital Sign and Body Weight (SAF)

- Wilcoxon 2-sample test

14.3.5.2. Box plots of Vital Sign and Body Weight

Figure 14.3.5.2.1 Box plots of Vital Sign and Body Weight (SAF)

14.3.6 ECG

14.3.6.1. Summary of 12-lead ECG Abnormalities

Table 14.3.6.1.1 Summary of 12-lead ECG Abnormalities (SAF)

- Fisher's exact test

14.3.6.2. Shift Table of ECG Abnormalities

Table 14.3.6.2.1 Shift Table of 12-lead ECG Abnormalities (SAF)

14.3.7 C-SSRS

14.3.7.1. Summary of C-SSRS

For the following items, the number of subjects who became "yes" at least once after administration in the treatment period is totaled.

- Suicidal ideation
- Suicidal behavior
- Suicidal ideation or behavior

Table 14.3.7.1.1 Summary of C-SSRS (SAF)

14.3.7.2. Shift Table of C-SSRS

The following items are summarized. The evaluation will be "yes" if it becomes "yes" at least once after administration in the treatment period.

- No suicidal ideation or behavior
- Suicidal ideation *
- Suicidal behavior *

*: If both are “yes”, "Suicidal behavior" is assumed.

Table 14.3.7.2.1 Shift Table of C-SSRS (SAF)

14.3.8 Concomitant Drugs

14.3.8.1. Summary of Concomitant Drugs

Concomitant Drugs are summarized by ATC level 2 and Preferred Name in WHO-DDs.

Table 14.3.8.1.1 Summary of Concomitant Drugs (SAF)

14.4 Pharmacokinetics

14.4.1 Pharmacokinetics

14.4.1.1. Descriptive Statistics of Plasma desvenlafaxine concentration

Table 14.4.1.1.1 Descriptive Statistics of Plasma desvenlafaxine concentration (OC)
(Pharmacokinetic analysis set)

15 Reference List

Not applicable to the SAP

16 Appendix

16.1 Study Information

Not applicable to the SAP

16.2 Subject Data Listings

16.2.1 Withdrawn Subjects

Table 16.2.1.1 Listing of Withdrawals

16.2.2 Protocol Deviations

Table 16.2.2.1 Listing of Protocol Deviations

16.2.3 Subjects Excluded From the Efficacy Analysis

Table 16.2.3.1 Listing of Subjects Excluded From the FAS and PPS

16.2.4 Background Factors

Table 16.2.4.1 Listing of Background Factors

16.2.5 Covariates Measured after Randomization

Table 16.2.5.1 Listing of Extent of Exposure to Study Drug

Table 16.2.5.2 Listing of Concomitant Drugs

Table 16.2.5.3 Listing of Concomitant Therapies

16.2.6 Individual Efficacy Response Data

Table 16.2.6.1 Listing of Efficacy Endpoints

16.2.7 Adverse events

Table 16.2.7.1 Adverse Event Reclassification Table

Table 16.2.7.2 List of Adverse Events (Treatment and Follow-up period)

Table 16.2.7.3 List of Adverse Events (Run-in period)

16.2.8 Laboratory Measurements

Table 16.2.8.1 Listing of Laboratory Measurements

16.2.9 Vital Signs and Body Weight

Table 16.2.9.1 Listing of Vital Signs and Body Weight

16.2.10 ECG

Table 16.2.10.1 Listing of 12-lead ECG Abnormalities

16.2.11 C-SSRS

Table 16.2.11.1 Listing of C-SSRS

16.2.12 Pharmacokinetics

Table 16.2.12.1 Listing of Plasma desvenlafaxine concentration

Appendix1 : List of factors used for Subgroup/Stratification Analysis
(*d* indicates *discrete variables* and *c* indicates *continuous variables*)

Factors	Subgroup Analysis		Stratification Analysis
	14.2.1.1.4.1-3 14.2.1.1.7.1-3 14.2.1.2.2.1-3 14.2.4.1.3.1-3 14.2.4.1.6.1-3 14.2.4.2.2.1-3 14.3.1.2.1-3	14.3.1.4.1-2	14.2.1.1.3.1-2 14.2.4.1.2.1-2
6.1.1 Demographic Variables			
Sex (Male, Female)	d	d	d
Race (AMERICAN INDIAN OR ALASKA NATIVE, ASIAN(JAPANESE, NON-JAPANESE), BLACK OR AFRICAN AMERICAN, NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER, WHITE, MULTIPLE)			
Age (years)			c
Age (years)(20-29, 30-39, 40-49, 50-59, 60-64, 65<=)			
Age (years)(20-50, 51<=)	d		
Age (years)(20-64, 65<=)	d	d	
Height(cm)			
Body weight (kg) (at the start of the screening period)			c
BMI (kg/m2) (at the start of the screening period)			c
6.1.2 Other Factors			
Age at the onset of depression (year)			c
Period from onset of depression (month)			c
Number of depressive episodes (times)			c
Number of depressive episodes (times)(1, 2<=, unspecified)	d		
Duration of current depressive episode (month)			c
Duration of current depressive episode (month)(<6, 6 - <12, 12-18)	d		
Presence/absence of prior treatment with antidepressant drugs for current and past depressive episodes (No, Yes)	d		d
Presence/absence of concomitant use of hypnotic/sedative drugs and narcoleptics (within 2 months before the initial registration) (No, Yes)	d		d
Presence/absence of a history of treatment with antianxiety drug (within 2 months before the initial registration) (No, Yes)	d		d
Presence or absence of comorbidities (No, Yes)			
6.1.3 Baseline			
Total MADRS score (baseline)			
Total MADRS score (baseline)(<=30, 31<=)	d		
Total HAMD17 score (baseline)			
CGI-S (baseline)			
Total QIDS16-SR-J score (baseline)			
Total SDS score (baseline)			
6.2.1 Extent of Exposure to the investigational drug			
Duration of exposure of the investigational drug (days) (treatment period)			
Duration of exposure of the investigational drug (days) (treatment period)(1-7, 8-14, 15-28, 29-42, 43-56, 57<=)			
Compliance rate of the investigational drug (%) (treatment period)			
Compliance rate of the investigational drug (%) (treatment period)(<75%, 75%<=)			
Total exposure of the investigational drug (mg) (treatment period)			

Appendix 2：sample SAS Program

Notes

In principle, variable names in the program below confirm to CDISC ADaM standard. Parts of program that are unrelated to the analysis algorithm, such as processing and sorting of the data set and outputting to the TLFs, are omitted.

The dataset structure, variable names, populated value, etc. may differ from the actual analysis dataset.

(1) Table 14.2.1.1.1.1 MMRM Analysis of Change in total MADRS score from baseline (OC) (FAS)

*Program for comparison only at Week 8 is shown below.

```
*-TRT02PN：Treatment grp(1: 50mg grp, 2： 100 mg grp, 3： Placebo grp);
proc mixed data=ADEFF;
    where PARAMCD="MADRSTOT" and AVISITN in(1,2,4,6,8) and FASFL="Y" and
    DTYPE="OC";
    class TRT02PN AVISITN USUBJID;
    model CHG=BASE AVISITN TRT02PN TRT02PN*AVISITN/ddfm=kr;
    lsmeans TRT02PN*AVISITN;
    estimate "MD-120 50 mg grp – Placebo grp at Week 8"
    TRT02PN*AVISITN      0 0 0 0 1
                         0 0 0 0 0
                         0 0 0 0 -1
    TRT02PN 1 0 -1/ cl;
    estimate "MD-120 100 mg grp – Placebo grp at Week 8"
    TRT02PN*AVISITN      0 0 0 0 0
                         0 0 0 0 1
                         0 0 0 0 -1
    TRT02PN 0 1 -1/ cl;
    repeated AVISITN/subject=USUBJID type=un;
run;quit;
```

(2) Table 14.2.1.1.2.1 Tipping Point Analysis of Change in total MADRS score from baseline (OC) (Week 8) (FAS)

```
*-step 1：Imputing non-monotone missing values;
*-tr_MADRS：transposed dataset as 1 observation for each subject;
proc mi data=tr_MADRS seed=2970 nimpute=10 out=tr_MADRS_mono;
    by TRT02PN;
    mcmc impute=monotone;
    var v1 v2 v4 v6 v8; *-v1 v2 v4 v6 v8：total MADRS score at each timepoint;
run;

*-create flag variables for identifying monotone missing values
*-v1miss： (1：missing、0：observed);
data tr_MADRS_mono;
    set tr_MADRS_mono;
    if v1=. then v1miss=1; else v1miss=0;
    if v2=. then v2miss=1; else v2miss=0;
    if v4=. then v4miss=1; else v4miss=0;
    if v6=. then v6miss=1; else v6miss=0;
    if v8=. then v8miss=1; else v8miss=0;
run;

%macro tpa(sp);

*-Specifying sensitivity parameter (&sp.) from 0 to 5;
%do sp=0 %to 5;

*-step 2-1：Imputing monotone missing values;
proc mi data=tr_MADRS_mono seed=8229 nimpute=1 out=tr_MADRS_imp;
    class TRT02PN;
    monotone reg(/detail);
    var TRT02PN v0 v1 v2 v4 v6 v8;
run;

*-step 2-2：add sensitivity parameter to the imputed value;
data tr_MADRS_adj;
    set tr_MADRS_imp;
    if v1miss=1 then v1=v1+&sp.;
    if v2miss=1 then v2=v2+&sp.;
    if v4miss=1 then v4=v4+&sp.;
    if v6miss=1 then v6=v6+&sp.;
    if v8miss=1 then v8=v8+&sp.;
run;

*-Converting transposed dataset into Basic Data Structure and calculating change
in total MADRS score (the program is omitted);
```

```
*-step 3：Applying the same MMRM model as the Primary Analysis ;
ods output Estimates=tpa_diff01;
proc mixed data=ADEFF_tpa;
    by _Imputation_;
    class TRT02PN AVISITN USUBJID;
    model CHG=BASE AVISITN TRT02PN TRT02PN*AVISITN/ddfm=kr;
    lsmeans TRT02PN*AVISITN;
    estimate "MD-120 50 mg grp – Placebo grp at Week 8"
    TRT02PN*AVISITN      0 0 0 0 1
                         0 0 0 0 0
                         0 0 0 0 -1
    TRT02PN 1 0 -1/ cl;
    estimate "MD-120 100 mg grp – Placebo grp at Week 8"
    TRT02PN*AVISITN      0 0 0 0 0
                         0 0 0 0 1
                         0 0 0 0 -1
    TRT02PN 0 1 -1/ cl;
    repeated AVISITN/subject=USUBJID type=un;
run;quit;

proc sort data=tpa_diff01;
    by Label;
run;

*-step 3：Combining estimates of adjusted mean differences;
proc mianalyze data=tpa_diff01;
    by Label;
    modeleffects Estimate;
    stderr StdErr;
run;
%end;
%mend;

%tpa;
```

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Date of change Version Person who changed	Change No.	Section	Changes and Reasons
2022/9/14 Ver1.0 → ver2.0 [redacted]	※	Unless otherwise noted, the section numbers given in the main text shall be the most recent version (ver2.0).	
	1	1 Study Director and Team	Changed people responsible The study director and the Person Responsible for Data Management were changed. [Reason] Responding to changes in the person responsible for the preparation of the SAP.
	2	2.6.2 Sample Size Rationale	Corrected minor error Hypothesis 1/Hypothesis 2 was added. [Reason] To correct omissions from the protocol.
	3	4.2.2 Data Sets Obtained on or after Unblinding	Corrected minor error The section name in 4.2.2 was changed from "Data Sets Obtained after Unblinding" to "Data Sets Obtained on or after Unblinding". [Reason] To correct minor errors.
	4	6.1 Background Factors 6.2 Covariates measured after randomization	Corrected minor error The unit was replaced before the assessment time point. [Reason] To correct minor errors.
	5	6.2.1 Extent of Exposure to the investigational drug Appendix 1	Removed analysis "Number of days of the investigational drug administration" was deleted. [Reason] It couldn't be identified from the CRF.
	6	6.2.1 Extent of Exposure to the investigational drug	Changed derivation The derivation for "compliance rate of the investigational drug" and "total exposure of the investigational drug" were changed. [Reason] In conjunction with the data collection methods of this study.

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Date of change Version Person who changed	Change No.	Section	Changes and Reasons
	7	7.1.15 Total SDS score	Changed definition The following rule was added to "(1) Definition of a formula or derivation". ・If “I have not worked/studied at all during the past week for reasons unrelated to the disorder” is selected, total SDS score will be handled as a missing value [Reason] To consider for use in CSR.
	8	7.1.17 SDS subscale 7.1.18 Change in SDS subscale from baseline	Added endpoint SDS subscales and their changes from baseline were added to endpoints. [Reason] To consider for use in CSR.
	9	7.2.2 Timing of withdrawal of treatment	Added category of endpoint "Not administered" was added to the category of "Timing of withdrawal of treatment." [Reason] To consider for use in CSR.
	10	7.3.4 Adverse Events Resulting in Treatment Interrupted	Added endpoint "Adverse Events Resulting in Treatment Interrupted" was added. [Reason] To consider for use in CSR.
	11	7.3.5 Common Adverse Events	Changed definition of endpoint The definition was changed as follows. *(Before change) Adverse events (PT) that occurred in 5% or more of either group during the treatment and follow-up periods* *(After change) Adverse events (PT) that occurred in 5% or more of either group during the aggregation period* [Reason] To consider for use in CSR.
	12	7.5 Vital signs and body weight	Added analysis For measured values and changes in vital signs and body weight, the assessment at Week 1 of the follow-up period was added. [Reason] To consider for use in CSR.

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Date of change Version Person who changed	Change No.	Section	Changes and Reasons
	13	7.8.1 Plasma desvenlafaxine concentration (ng/mL)	Changed analysis method The handling for values below the lower limit of quantification was changed from "handled as missing" to "handled as 0." [Reason] To consider for use in CSR. Corrected minor error Unit (ng/mL) were added to the section title. [Reason] To correct omissions.
	14	9.2.1 LOCF method	Changed analysis method The target of LOCF imputation was changed as follows. *The value used to LOCF imputation will include ...* *(Before change) all data that meet the data adoption conditions from the date of the first dose of the investigational drug in the treatment period (not included on the same day), regardless of whether or not they are included in the data adoption period.* *(After change) all data that meet the data adoption conditions from the date of the first dose of the investigational drug in the treatment period (including the same day), regardless of whether or not they are included in the data adoption period.* [Reason] To ensure consistency with the protocol and the handling plan.
	15	14.1.1.1. Disposition of Subjects 14.1.1.4. Structure of Safety Analysis Populations	Changed analysis method In "Table 14.1.1.1.1 Disposition of Subjects in the Study (1st enrolled subjects)", the tabulation of "discontinued screening period" was added. In addition, the tabulation of "discontinued follow-up period" was divided into (Before Week 1 visit) and (After Week 1 visit). In Table 14.1.1.4.1 Structure of Safety Analysis Population (2nd enrolled subjects), the tabulation of "Randomized subjects" was added. [Reason] To consider for use in CSR.

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Date of change Version Person who changed	Change No.	Section	Changes and Reasons
	16	14.2.2.1.1. GEE analysis of response evaluated by total MADRS score 14.2.2.1.2. Logistic regression of response evaluated by total MADRS score	Added annotation In the statistics to be calculated, a sentence "※If at least one of the two groups being compared has no response cases, these statistics are not calculated." was added. [Reason] To consider the situation in which the estimation is impossible.
	17	14.2.7.1.1. MMRM Analysis of CGI-I	Deleted analysis The analysis of the change from baseline in CGI-I was deleted. [Reason] It couldn't be calculated.
	18	14.2.11.1.1. MMRM Analysis of Change in total SDS score from baseline 14.2.11.1.2. ANCOVA Analysis of Change in total SDS score from baseline 14.2.11.2.1. Descriptive Statistics of total SDS score and Change in total SDS score from baseline	Added analysis An analysis of SDS subscale was added. [Reason] To consider for use in CSR.
	19	14.3.1.6. Summary of Adverse Events by SOC and PT by timing of occurrence	Changed analysis The reference date used to derive the number of days to completion of follow-up was changed from "date of the first dose of the investigational drug in treatment period" to "date of the first dose of the investigational drug in treatment period or follow-up period." [Reason] To perform the tabulation according to the onset time in the follow-up period.
	20	14.3.1.7. Common Adverse Events	Added analysis Difference in incidence rates (3 ways) and two-sided 95% CI were added to Calculated statistics. Table 14.3.1.7.5 Summary of Common Adverse Events by PT (Follow-up period) (SAF in Follow-up period) was added. [Reason] To consider for use in CSR.

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Date of change Version Person who changed	Change No.	Section	Changes and Reasons
	21	14.3.1.8. Notable Adverse Events	Added analysis Difference in incidence rates (3 ways) and their two-sided 95 CI were added to Calculated statistics. [Reason] To consider for use in CSR.
	22	14.3.2 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events 14.3.2.3. Adverse Events Resulting in Treatment Withdrawal	Changed analysis title The analysis title was changed as follows. <Not applicable for the english version of SAP> [Reason] To consider for use in CSR.
	23	14.3.2.4. Adverse Events Resulting in Treatment Interrupted	Added analysis The following analysis was added. Table 14.3.2.4.1 Listing of Adverse Events Resulting in Treatment Interrupted Table 14.3.2.4.2 Summary of Adverse Events Resulting in Treatment Interrupted by SOC and PT (Treatment period) (SAF) [Reason] To consider for use in CSR.
	24	14.3.4.2. Laboratory Abnormalities	Corrected minor error The analysis method of "Table 14.3.4.2.1 Shift Table of Laboratory Abnormalities (SAF)" was changed as follows. *(Before change) Column variables: Minimum and maximum values after administration* *(After change) Column variables: Minimum and maximum values after administration in the treatment period* [Reason] To clarify the analysis method.
	25	14.3.6.1. Summary of 12-lead ECG Abnormalities	Added analysis For Table 14.3.6.1.1 Summary of 12-lead ECG Abnormalities (SAF), Fisher exact test was added. [Reason] To correct omissions.

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Date of change Version Person who changed	Change No.	Section	Changes and Reasons
	26	14.3.7.1. Summary of C-SSRS	Corrected minor error The analysis method was changed as follows. *(Before change) The number of subjects who became "yes" at least once after administration is totaled.* *(After change) The number of subjects who became "yes" at least once after administration in the treatment period is totaled.* [Reason] To clarify the analysis method.
	27	14.3.7.2. Shift Table of C-SSRS	Corrected minor error The analysis method was changed as follows. *(Before change) The evaluation shall be "yes" if it becomes "yes" at least once after administration.* *(After change) The evaluation shall be "yes" if it becomes "yes" at least once after administration in the treatment period.* [Reason] To clarify the analysis method.
	28	14.3.8.1. Summary of Concomitant Drugs	Added analysis The following analysis was added. Table 14.3.8.1.1 Summary of Concomitant Drugs (SAF) [Reason] To consider for use in CSR.
	29	Other minor changes were made.	