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

Study Protocol

Mochida Pharmaceutical Co., Ltd.

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[Confidentiality]

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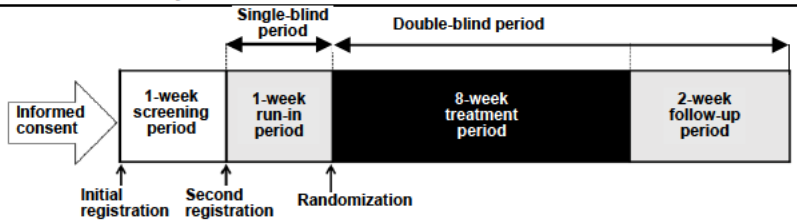
[Abbreviations used in this study protocol]

Abbreviations	English terms
ALP	Alkaline phosphatase
ALT (GPT)	Alanine aminotransferase (glutamic-pyruvic transaminase)
AST (GOT)	Aspartate aminotransferase (glutamic-oxaloacetic transaminase)
CGI-I	Clinical Global Impression-Improvement Scale
CGI-S	Clinical Global Impression-Severity Scale
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	Cytochrome P450
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
eCOA	Electronic Clinical Outcome Assessment
EDC	Electronic Data Capture
FAS	Full Analysis Set
FDA	Food and Drug Administration (U.S.)
γ-GTP	γ-Glutamyl transpeptidase
HAMD17	Hamilton Depression Rating Scale, 17 items
HbA1c	Glycosylated Hemoglobin
HDL	High Density Lipoprotein
ITT	Intention-To-Treat
JAN	Japanese Accepted Names for Pharmaceuticals
LDL	Low Density Lipoprotein
LOCF	Last Observation Carried Forward
MADRS	Montgomery Åsberg Depression Rating Scale
MAO	Monoamine oxidase
MedDRA/J	Medical Dictionary for Regulatory Activities/Japanese version
M.I.N.I.	Mini International Neuropsychiatric Interview
NaSSA	Noradrenergic and Specific Serotonergic Antidepressant
PPS	Per Protocol Set
$QIDS_{16}$-SR-J	The 16-item Quick Inventory of Depressive Symptomatology self-report version
SDS	Sheehan Disability Scale
SNRI	Serotonin Noradrenaline Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
TMS	Transcranial Magnetic Stimulation

[Terms in this study protocol]

Terms	Explanations
MD-120	Development code of the investigational drug of this clinical study Nonproprietary name: Desvenlafaxine succinate hydrate (JAN) Overseas proprietary name: PRISTIQ®
Screening period	Period from "the start of any observation or test scheduled at the initial registration" to "the day of the second registration," 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", 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 premature termination", 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 visit at the time of premature termination" to "the time of completion of all observation and tests scheduled at the end of follow-up period" or "the time of completion of all observation and tests scheduled at the visit at the time of premature termination during follow-up period*", when the post-treatment safety is evaluated.
Baseline	At the end of run-in period
Amount of change	(Score at evaluation timepoint) - (Baseline score)
Response	[MADRS] Criteria for response: "Total MADRS score at evaluation timepoint is ≤50% of baseline score." [HAMD17] Criteria for response: "Total HAMD17 score at evaluation timepoint is ≤50% of baseline score." [CGI-I] Criteria for response: "Evaluated as "1. Very much improved" or "2. Much improved" at evaluation timepoint"
Remission	[MADRS] Criteria for remission: "Total MADRS score at evaluation timepoint is ≤10." [HAMD17] Criteria for remission: "Total HAMD17 score at evaluation timepoint is ≤7."

* The time of premature termination before Week 1 visit during follow-up period.

Study title	
Study title	A Placebo-controlled Study of MD-120 in Depression Patients
Protocol code	MD120101
Protocol synopsis	
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.
Study type	Confirmatory study
Study design	A randomized, parallel-group, multicenter, double-blind, placebo-controlled study
Anticipated period of study participation	
Treatment groups	At the time of randomization, subjects will be randomly assigned to any of the following three groups under the double-blind condition. (1) Placebo group (2) MD-120 50 mg group (3) MD-120 100 mg group
Target sample size	594 subjects as FAS (198 subjects per group)
Dosage and administration	Administration: Once-daily oral administration Dosage: (1) Run-in period All subjects will receive the placebo (2 placebo tablets) from the start to the end of run-in period. (2) Treatment period [Placebo group] • The subjects will receive the placebo (2 placebo tablets) from the start to the end of treatment period. [MD-120 50 mg group] • The subjects will receive MD-120 50 mg (1 MD-120 50 mg tablet) and the placebo (1 placebo tablet) from the start to the end of treatment period. [MD-120 100 mg group] • The subjects will receive one MD-120 50 mg (1 MD-120 50 mg tablet) and the placebo (1 placebo tablet) from the start to Week 1 visit during treatment period. • The subjects will receive two MD-120 100 mg (2 MD-120 50 mg tablets) from the day following Week 1 visit to the end of treatment period.

	(3)Follow-up period [Placebo group] • The subjects will receive the placebo (2 placebo tablets) from the start to Week 1 visit of follow-up period. [MD-120 50 mg group] • The subjects will receive the placebo (2 placebo tablets) from the start to Week 1 visit of follow-up period. [MD-120 100 mg group] • The subjects will receive MD-120 50 mg (1 MD-120 50 mg tablet) and the placebo (1 placebo tablet) from the start to Week 1 visit of follow-up period.
Primary endpoint	(1) Efficacy Change in total MADRS score from baseline to Week 8 visit during treatment period (2) Safety Adverse events during treatment period and follow-up period
Secondary endpoint	(1) Efficacy • Response evaluated by total MADRS score at Week 8 visit during treatment period (Criteria for response: "Total MADRS score at Week 8 visit during treatment period is ≤50% of baseline score.") • Remission evaluated by total MADRS score at Week 8 visit during treatment period (Criteria for remission: "Total MADRS score at Week 8 visit during treatment period is ≤10.") • Change in total HAMD17 score from baseline to Week 8 visit during treatment period • Response evaluated by total HAMD17 score at Week 8 visit during treatment period (Criteria for response: "Total HAMD17 score at Week 8 visit during treatment period is ≤50% of baseline score.") • Remission evaluated by total HAMD17 score at Week 8 visit during treatment period (Criteria for remission: "Total HAMD17 score at Week 8 visit during treatment period is ≤7.") • CGI-I at Week 8 of the treatment period • Response evaluated by CGI-I at Week 8 visit during treatment period (Criteria for response: "Evaluated as "1. Very much improved" or "2. Much improved" at Week 8 visit during treatment period") • Change in CGI-S from baseline to Week 8 visit during treatment period • Change in total $QIDS_{16}$-SR-J score from baseline to Week 8 visit during treatment period • Change in total SDS score from baseline to Week 8 visit during treatment period

	(2) Safety 1) Adverse drug reactions (ADRs) during treatment period and follow-up period 2) Adverse events and ADRs during treatment period 3) Adverse events and ADRs during follow-up period
Inclusion criteria (At the initial registration)	(1) Patients who have consented in writing to participate in this clinical study (2) Outpatients aged ≥20 at the time of informed consent (3) Patients with "depression" who have experienced non-psychotic or non-mixed single or repeated episode, which has been diagnosed according to DSM-5 (for DSM-5-based diagnosis, Mini-International Neuropsychiatric Interview [M.I.N.I.] version 7.0.2 will be used as a diagnostic aid tool) (4) Patients in whom the current depressive episode has persisted for ≥3 months and ≤18 months if it is single or for ≥1 months and ≤18 months if it is recurrent, according to DSM-5 (5) Patients with the total score of ≥20 in Hamilton Depression Rating Scale (HAMD) 17 and the sub-score of ≥2 for Item 1 (depressed mood) (6) Patients with the score of ≥4 in CGI-S (7) Patients with the total score of ≥16 in Quick Inventory of Depressive Symptomatology $(QIDS)_{16}$-SR-J
Exclusion criteria (At the initial registration)	(1) Patients judged by the (sub-)investigator to have any of the following disorders classified according to DSM-5 (using a diagnostic aid tool of M.I.N.I. version 7.0.2 if appropriate) • Intellectual disabilities • Autism spectrum syndrome/Autism spectrum disorder • Attention deficit and hyperkinesia/Attention deficit and hyperactivity disorder • Schizophrenia spectrum disorder and other psychotic disorders • Bipolar and related disorders • Obsessive disorder syndrome and related syndromes/Obsessive compulsive disorder and related disorders • Psychic trauma and stress-related disorders • Disassociation syndrome/dissociative disorders • Eating behavior disorders and eating disorders • Substance-related disorders (except for those caused by tobacco or caffeine) • Neurocognitive deficiency • Personality disorders (2) Patients concurrently with any of the following disorders classified according to DSM-5, which is also positioned as the main disorder by the (sub-)investigator (using a diagnostic aid tool of M.I.N.I. version 7.0.2 if appropriate) • Anxiety/Anxiety disorders (3) Patients judged by the (sub-)investigator to have a past history of any of the following disorders classified according to DSM-5 (using a diagnostic aid tool of M.I.N.I. version 7.0.2 if appropriate)

	• Schizophrenia spectrum disorder and other psychotic disorders • Bipolar and related disorders • Substance-related disorders (except for those caused by tobacco or caffeine) (4) Patients meeting any of the followings: • Patients who presented a certain form of followings "suicidal behavior" (suicide attempt, interrupted suicide attempt, withdrawn suicide attempt, and preparatory behavior) within 1 year before the start of the screening period as assessed according to Columbia-Suicide Severity Rating Scale (C-SSRS) • Patients meeting B14 or B16 under "B. Suicidal ideation, Self-injurious and Suicidal behavior" or B18 within past 12 months in M.I.N.I. version 7.0.2 • Patients with the sub-score of ≥3 for Item 11 (suicide) in HAMD17 • Patients with the sub-score of ≥5 for Item 10 (Thought of Death or Suicide) in Montgomery-Asberg Depression Scale (MADRS) • Patients with the sub-score of ≥3 for Item 12 (Suicidal ideation) in $QIDS_{16}$-SR-J • Patients judged by the (sub-)investigator to be at a high risk of suicide (5) Patients who have a first-degree relative (parent, sibling, and child) with bipolar and related disorders (6) Patients with a past history of or co-existing convulsive disorder such as epilepsy (excluding fever seizure) (7) Patients with a past history of or co-existing acute angle closure glaucoma or elevated intraocular pressure (8) Patients who have received desvenlafaxine (9) Patients who received venlafaxine for the current depressive episode (10) Patients with serious drug allergy or hypersensitivity, or hypersensitivity to venlafaxine or desvenlafaxine (11) Patients who received other investigational drugs within 16 weeks before the start of the screening period (12) Patients who received but were not responsive to two or more antidepressants given at an adequate dose (in the range of approved dose excluding initial low dose, and doctors who treat the patients judged to be adequate) for at least 4 weeks for the current or past depressive episode (13) Patients who have undergone electroconvulsive therapy or transcranial magnetic stimulation (TMS) therapy (14) Patients with a history of hospitalization owing to psychiatric disorders excluding depression (15) Patients who received any antipsychotics within 2 weeks before the start of screening period (or within 6 months for a depot formulation) (16) Patients who received a hypnotic/sedative (excluding zopiclone, zolpidem, and eszopiclone) within 2 weeks before the start of screening period

	(17) Patients with a co-existing serious hepatic, renal, hematological, respiratory, gastrointestinal, or cardiovascular disease, or metabolism/electrolytes abnormality (18) Female patients who are or may be pregnant, are breast-feeding, or male and female patients who are intend to conceive during the study period (19) Patients who are otherwise judged by the (sub-) investigator to be ineligible for this clinical study
Inclusion criteria (At the second registration)	(1) Patients whose depressive episode at the time of the initial registration persists (2) Patients with the total score of ≥20 in Hamilton Depression Rating Scale (HAMD) 17 and the sub-score of ≥2 for Item 1 (depressed mood) (3) Patients with the score of ≥4 in CGI-S (4) Patients with the total score of ≥16 in Quick Inventory of Depressive Symptomatology ($QIDS_{16}$-SR-J
Exclusion criteria (At the second registration)	(1) Patients meeting any of the followings: • Patients who presented a certain form of followings "suicidal behavior" (suicide attempt, interrupted suicide attempt, withdrawn suicide attempt, and preparatory behavior) between the initial and second registrations as assessed according to C-SSRS • Patients with the sub-score of ≥3 for Item 11 (suicide) in HAMD17 • Patients with the sub-score of ≥5 for Item 10 (Suicidal Thoughts) in Montgomery-Asberg Depression Scale (MADRS) • Patients with the sub-score of ≥3 for Item 12 (Thought of Death or Suicide) in $QIDS_{16}$-SR-J • Patients judged by the (sub-)investigator to be at a high risk of suicide (2) Patients who have received a concomitant drug or therapy prohibited from the start of screening period (3) Patients who have deviated from the conditions for concomitant use of hypnotic/sedative that are allowed for use from the start of screening period (4) Patients determined by the (sub-)investigator to be ineligible for the study based on the result of diagnosis confirmation by the Clinical data analytics committee regarding the assessment at the time of the initial registration by the (sub-)investigator for the diagnosis (5) Patients who are otherwise judged by the (sub-) investigator to be ineligible for this clinical study
Inclusion criteria (At randomization)	(1) Patients whose depressive episode at the time of the initial registration persists (2) Patients with the total score of ≥20 in Hamilton Depression Rating Scale (HAMD) 17 and the sub-score of ≥2 for Item 1 (depressed mood) (3) Patients with the score of ≥4 in CGI-S

	(4) Patients with the total score of ≥16 in Quick Inventory of Depressive Symptomatology $(QIDS)_{16}$-SR-J
Exclusion criteria (At randomization)	(1) Patients meeting any of the followings: • Patients who presented a certain form of followings "suicidal behavior" (suicide attempt, interrupted suicide attempt, withdrawn suicide attempt, and preparatory behavior) between the second registration and randomization as assessed according to C-SSRS • Patients with the sub-score of ≥3 for Item 11 (suicide) in HAMD17 • Patients with the sub-score of ≥5 for Item 10 (Suicidal Thoughts) in Montgomery-Asberg Depression Scale (MADRS) • Patients with the sub-score of ≥3 for Item 12 (Thought of Death or Suicide) in $QIDS_{16}$-SR-J • Patients judged by the (sub-)investigator to be at a high risk of suicide (2) Patients whose total score in HAMD17 deteriorated or improved by ≥25% from the second registration (3) Patients who missed taking the investigational drug on ≥2 days during run-in period (4) Patients who have received a concomitant drug or therapy prohibited from the start of screening period (5) Patients who have deviated from the conditions for concomitant use of hypnotic/sedative that are allowed for use from the start of screening period (6) Patients determined by the (sub-)investigator to be ineligible for the study based on the result of diagnosis confirmation by the Clinical data analytics committee regarding the assessment at the time of the initial registration by the (sub-)investigator for the diagnosis (7) Patients who are otherwise judged by the (sub-) investigator to be ineligible for this clinical study
Prohibited concomitant drugs	Concomitant drugs prohibited from the start of screening period to the end of follow-up period (1) MAO inhibitors (2) Investigational drugs other than MD-120 (3) Desvenlafaxine and venlafaxine other than MD-120 Concomitant drugs prohibited from the start of screening period to the completion of all observation and tests scheduled at the end of treatment period (4) Antipsychotic drugs (5) Antianxiety drugs (6) Hypnotic/sedative drugs (excluding zopiclone, zolpidem, and eszopiclone) (7) Hypnotic drugs (8) Antidepressant drugs (9) Antimanic drugs (10) Antiepileptic drugs (11) Antiparkinson drugs

	(12) Chinese medicines indicated for treatment of anxiety, insomnia, and depressed mood (13) Drugs containing serotonin precursor (L-tryptophan, 5-hydroxytryptophan, etc.) (14) Drugs containing tramadol (15) Triptan drugs
Prohibited concomitant therapies	Concomitant therapies prohibited from the start of screening period to the end of follow-up period (1) Electroconvulsive therapy (2) Transcranial magnetic stimulation (TMS) therapy (3) Supplement containing St. John 's Wort as the active ingredient Concomitant therapies prohibited from the start of screening period to the completion of all observation and tests scheduled at the end of treatment period (4) Systematized psychotherapies (including cognitive behavior therapies)
Allowed concomitant drugs	Subjects receiving zopiclone, zolpidem, or eszopiclone, at 2 weeks before the start of the screening period will be allowed to concomitantly use such hypnotics/sedatives. They will be allowed to use only 1 drug from the start of screening period to the completion of all observation and tests scheduled at the end of treatment period when needed and on ≤3 days per week, but prohibited to use it within 24 hours before each scheduled visit. The dosage shall not exceed 7.5 mg/night for zopiclone, 5 mg/night for zolpidem, and 2 mg/night for eszopiclone.
Statistical analysis	Analysis of the primary efficacy endpoint: • The efficacy analysis will be mainly performed on the full analysis set (FAS). • 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 the change in total MADRS score from baseline to each evaluation timepoint as a response variable; the treatment group, assessment timepoint, and the interaction between the treatment group and assessment timepoint as fixed effects, 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 [redacted]
Study period	April 2020 to December 2022

[Observation and test, and evaluation schedule]

		Screening period (1 week)			Single-blind period: Run-in period (1 week)		Double-blind period: Treatment period (8 weeks)						Follow-up period (2 weeks)	
		Initial registration: Start		Second registration: End	Start	End or premature termination	Randomization: Start	Week 1	Week 2	Week 4	Week 6	Week 8 or premature termination	Week 1 or premature termination[a]	End or premature termination[b]
Visit (N)		1		2	-	3	-	4	5	6	7	8	9	10
Informed consent	✓													
Inclusion and exclusion criteria		✓		✓		✓[g]								
Subject baseline characteristics[c]		✓												
M.I.N.I.		✓												
DSM-5 (Diagnosis of depression)		✓												
Diagnosis confirmation		✓												
MADRS		✓		✓		✓[g]		✓	✓	✓	✓	✓		
HAMD17		✓		✓		✓[g]			✓	✓		✓		
CGI-S		✓		✓		✓[g]		✓	✓	✓	✓	✓		
CGI-I								✓	✓	✓	✓	✓		
$QIDS_{16}$-SR-J		✓		✓		✓[g]		✓	✓	✓	✓	✓		
SDS		✓				✓[g]				✓		✓		
C-SSRS		✓		✓		✓[g]		✓	✓	✓	✓	✓	✓	
Vital signs and body weight		✓		✓		✓[g]		✓	✓	✓	✓	✓	✓	
Body height[d]		✓												
Drug concentration measurement									✓	✓		✓		
General laboratory test			✓[f]						✓	✓		✓		
Pregnancy test[e]		✓												
Standard 12-lead ECG		✓				✓[g]						✓		
Concomitant therapies		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adverse events					✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Dispensing and retrieval of investigational drug				✓		✓		✓	✓	✓	✓	✓	✓	

a: The time of premature termination before Week 1 visit during follow-up period.
b: The time of premature termination after Week 1 visit during follow-up period.
c: Subject baseline characteristics: Gender, race, date of birth, date of informed consent, height, time of the initial depression onset, frequency of depressive episodes, the start time of the current depressive episode, the applicability of the DSM-5 criteria to each depressive symptom, a history of treatment with antidepressant drugs (chemical names)

for the current and past depressive episodes, a history of treatment with hypnotics/sedatives and (chemical names), and a history of treatment with antianxiety drug (presence/absence) (See "13.1 Subject baseline characteristics").

d: Included in "Subject baseline characteristics".
e: Performed only for premenopausal female subjects.
f: The urinalysis is allowed to be performed before the initial registration as a non-invasive test.
g: Not performed at the time of premature termination

[Planned day for visits and acceptable window]

Visit	Planned day	Planned day (acceptable window)
1	Start of screening period	-
2	End of screening period	Day 8 (+3) starting from the day of visit that is Day 1.
-	Start of run-in period (no visit)	The next day of the second registration
3	End of run-in period or the time of premature termination	Day 7 (±1) starting from the start of run-in period that is Day 1.
-	Start of treatment period (no visit)	The next day of randomization
4	Week 1 visit during treatment period	Day 7 (±1) starting from the start of treatment period that is Day 1
5	Week 2 visit during treatment period	Day 14 (±3) starting from the start of treatment period that is Day 1
6	Week 4 visit during treatment period	Day 28 (±3) starting from the start of treatment period that is Day 1
7	Week 6 visit during treatment period	Day 42 (±3) starting from the start of treatment period that is Day 1
8	Week 8 visit during treatment period or the time of premature termination	Day 56 (±3) starting from the start of treatment period that is Day 1
9	Week 1 visit during follow-up period or the time of premature termination	Day 7 (±1) starting from the next day of the Week 8 visit during treatment period or the visit at premature termination that is Day 1
10	End of follow-up period or the time of premature termination	Day 7 (+7) starting from the next day of the Week 1 visit during follow-up period or the visit at premature termination that is Day 1

[Details of general laboratory test and vital signs]

Test		Test items
General laboratory test	Hematology	White blood cell count (WBC), red blood cell count (RBC), hemoglobin, hematocrit, and platelet count
	Blood biochemistry	AST (GOT), ALT (GPT), ALP, gamma-GTP, total bilirubin, total protein, albumin, urea nitrogen, creatinine, total cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol, blood glucose, HbA1c, sodium, potassium, and chloride
	Urinalysis (qualitative)	Urine protein, urine glucose, and occult blood in urine
Vital signs		Sitting blood pressures (systolic/diastolic), and pulse rates

Table of Contents

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. Background information

2.1 Name and explanation of the investigational drug

[Investigational ingredient code]

MD-120

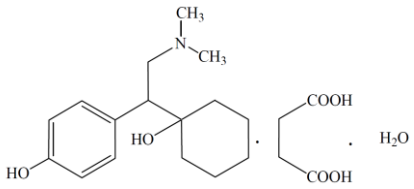
[Nonproprietary name (active ingredient)]

Desvenlafaxine succinate hydrate (JAN)

[Chemical name]

RS-4-[2-dimethylamino-1-(1-hydroxycyclohexyl)ethyl] phenol (free base)

[Structural formula]



[Molecular formula and weight]

Molecular formula: $C_{16}H_{25}NO_2$ (free base), $C_{16}H_{25}NO_2 \cdot C_4H_6O_4 \cdot H_2O$ (succinate monohydrate)

Molecular weight: 263.38 (free base), 399.48 (succinate monohydrate)

[Storage method]

Store it away from direct sunlight at room temperature

[Dosage form and appearance]

Extended-release tablet: A pale red square-shaped film-coated tablet with a pyramidal shape on one side

2.2 Background for this clinical study

2.2.1 Background of and treatment method for the target disorder

Depression is a psychiatric disorder which causes the degradation of the quality of life associated with psychiatric symptoms such as depressed mood or loss of interest or joy and somatic symptoms such as weight decreased or sleeplessness. The life-time morbidity rate of depression is 6% in Japan and twice higher in females than in males[1)]. Depression is common not only among young adults but also among middle-aged and senior citizens in Japan[1)]. According to the MHLW patient survey in 2017, 0.495 million men and 0.781 million female receive treatment for their mood disorder including depression, and most common in the 40s of all age brackets[2)].

As basic treatment policies for depression, basic intervention are performed by supportive psychiatric therapy and psychological training at first, then drug therapy, somatic therapy, and psychiatric therapy are started as appropriate for the symptoms, for any severity of depression, mild, moderate, and severe. Drug therapy plays the central role for moderate to severe depression[3)].

Conventional drugs such as tricyclic and tetracyclic antidepressants and novel antidepressants such as SSRI, SNRI, and NaSSA are used as drug therapy for depression. According to the Japanese Society of Mood Disorders Guideline (hereinafter, the "JSMD Guideline"), novel antidepressants are primarily used as the first-line drugs in many cases from the aspect of tolerability[3]. Also, antidepressants are not used in combination unless otherwise specified and are switched to other antidepressants if an antidepressant used at an adequate dose for an adequate period is not adequately effective[3)]. Furthermore, depression treatment processes are classified into three phases, the acute phase when pathological depressed state attenuates to remission, the continuation phase when remission state is maintained for 3-6 months followed by recovery, and the maintenance phase following recovery. It is considered desirable to follow the patients for approximately 8 weeks to evaluate the treatment response to drug therapy in the acute phase treatment[3)].

2.2.2 Significance of development of MD-120

MD-120 is a preparation containing desvenlafaxine succinate, which is a succinate of metabolite of venlafaxine (Effexor®), and made to release the active ingredient slowly by the modification of desvenlafaxine succinate. MD-120 is classified as a SNRI like venlafaxine. As of May 2019, MD-120 is approved in 44 countries including the U.S., Canada, Australia, and South Korea for the treatment of major depressive disorder (MDD) at the recommended dose of 50 mg/day.

In Japan, 3 SNRIs (milnacipran hydrochloride, duloxetine hydrochloride, and venlafaxine hydrochloride) have been marketed; all of which need to be started with low dose and gradually increased to the conventional dose[4)-6)]. On the other hand, MD-120 is recommended to use at the clinically recommended dose from the first administration in overseas package insert[7)].

MD-120 whose main metabolic pathway is glucuronate conjugation is considered to have a lower risk of drug interaction than venlafaxine which is metabolized to desvenlafaxine via CYP2D6. Furthermore, the overseas package insert specifies that the dose of venlafaxine whose dose needs to be halved or less in patients with mild to severe hepatic function disorder because its blood concentration is increased as hepatic function disorder becomes severer[8)]. On the other hand, MD-120 showed no increase in its blood concentration according to the severity of hepatic function disorder in a clinical study in patients with hepatic function disorder, by which no dose adjustment is required, unlike venlafaxine[7)].

A U.S. clinical guideline recommends SSRI, SNRI, mirtazapine, and bupropion as drug therapies for depression and a Canadian clinical guideline recommends SNRI along with SSRI including duloxetine, venlafaxine, and MD-120 as the first-line drugs for depression treatment[9), 10)].

It has been reported that about 20% to 40% of depression patients receiving antidepressant medications obtain only partial improvement of their symptoms or no improvement at all[11)], as described in "2.2.1 Background of and treatment method for the target disorder", the antidepressant treatment procedures recommends to switch an antidepressant drug to other antidepressant drug if not responded well; therefore,

additional antidepressant drugs to select from should be beneficial for doctors and patients. It is considered significant to develop MD-120 in Japanese patients with depression since if MD-120 is verified effective and safe in Japanese patients with depression in this clinical study, MD-120 is expected to be one of the therapeutic options for depression treatment as in other countries.

2.2.3 History of development

[redacted]

This time, to re-verify the efficacy in Japanese patients with depression, we reviewed the study design and decided to perform this study in three treatment groups, the placebo group, 50 mg group, and 100 mg group, for verifying the efficacy and evaluating the safety of MD-120 in Japanese patients with depression.

See "MD-120 Investigator's Brochure" for details about the results from each of the studies.

2.3 Summary of known and potential risks and benefits in the subjects

2.3.1 Summary of risks

The following are safety-related study results and overseas Post-Marketing Safety Data from MD-120 in an overseas Phase I study in Japanese healthy female adults (Study 1200-US), a global clinical Phase III study in patients with MDD including Japanese patients (Study 3359-ww), and a Japanese long-term dosing study in Japanese patients with MDD who had completed Study 3359-ww (Study 3350). See "MD-120 Investigator's Brochure" for details about the safety-related study results from each of the studies and other clinical studies.

2.3.1.1 Overseas Phase I study (Study 1200-US)

[redacted]

2.3.1.2 Global clinical Phase III study (Study 3359-ww)

The placebo, MD-120 25 mg/day, and MD-120 50 mg/day were administered for 8 weeks after 10-day placebo run-in period in 699 patients with MDD including Japanese patients.

The incidence rate of adverse events during treatment period was 59.3% (137/231), 63.4% (147/232), and 68.6% (162/236), respectively, in the placebo group, 25 mg group, and 50 mg group. Adverse events observed at the incidence rate of ≥5% in any of the groups were nasopharyngitis, nausea, headache, dizziness, somnolence, and dry mouth (Table 2.3-2). Of these events, nasopharyngitis (1 subject) in the 25 mg group and dizziness and headache (each in 1 subject) in the 50 mg group were rated as severe. The other adverse events were rated mild or moderate.

No death was observed.

The incidence rate of serious adverse events other than death during run-in period, treatment period, and follow-up period was 1.3% (3/231), 0.4% (1/232), and 2.1% (5/236), respectively, in the placebo group, 25 mg group, and 50 mg group. Serious adverse events other than death were depression in 3 subjects (1 subject in the run-in period, 1 subject each in the placebo group and the 50 mg group in the treatment period), chest discomfort (1 subject in the run-in period), grand mal convulsion and pneumothorax (1 subject for each in the placebo group), post procedural complication (post-hernia surgery recurrence of right side inguinal hernia, 1 subject in the 25 mg group), peritonsillar abscess, pancreatic neuroendocrine tumour metastatic, hallucination, auditory, homicidal ideation, suicidal ideation, and suicide attempt (1

subject for each in the 50 mg group). All were severe in severity except chest discomfort, grand mal convulsion, and post procedural complication that were moderate in severity. The outcome was recovery for all except pancreatic neuroendocrine tumour metastatic.

The incidence rate of adverse events during run-in period, treatment period, and follow-up period was 2.6% (6/231), 3.4% (8/232), and 3.4% (8/236), respectively, in the placebo group, 25 mg group, and 50 mg group. Adverse event that required withdrawal of the clinical trial, which occurred in ≥2 subjects, was depression in 7 subjects (1 during run-in period and 2, 3, and 1 subject, respectively, in the placebo group, the 25 mg group, and the 50 mg group during treatment period), nausea in 3 subjects (1 during run-in period and 1 subject each in the 25 mg and 50 mg groups during treatment period), vomiting in 2 subjects (1 subject each in the placebo and 25 mg groups), and anxiety in 2 subjects (1 subject each in the 25 mg and 50 mg groups). All of these adverse events were rated either mild or moderate for except for depression as serious adverse events other than death, which occurred in 3 subjects (1 during run-in period and 1 each in placebo and 50 mg groups during treatment period). Also, outcomes were recovery in all subjects except for 2 with depression in the 25 mg group.

Table 2.3-2 Adverse events that occurred in ≥5% of subjects in any of the groups (Study 3359-ww, during treatment period)

Adverse events	Placebo group (n=231)	25 mg group (n=232)	50 mg group (n=236)
Nasopharyngitis	25 (10.8)	17 (7.3)	26 (11.0)
Nausea	10 (4.3)	15 (6.5)	26 (11.0)
Headache	16 (6.9)	19 (8.2)	19 (8.1)
Dizziness	5 (2.2)	11 (4.7)	17 (7.2)
Somnolence	9 (3.9)	8 (3.4)	13 (5.5)
Dry mouth	8 (3.5)	13 (5.6)	6 (2.5)

Percentage of subjects with adverse events (%)

2.3.1.3 Japanese long-term dosing study (Study 3350)

MD-120 was administered at a flexible dose of 25–100 mg/day for 10 months to 304 Japanese subjects who completed Study 3359-ww.

The incidence rate of adverse events during treatment period was 78.9% (240/304). Adverse events that occurred in ≥5% of subjects were nasopharyngitis, somnolence, headache, nausea, diarrhea, dizziness, abdominal pain upper, weight increased, back pain, and constipation (Table 2.3-3). Of these events, somnolence (1 subject) was the only severe event, and the other adverse events were rated mild or moderate.

1 subject who had suicide and died, which was judged by the clinical investigator to be causally unrelated with the investigational drug.

The incidence rate of serious adverse events other than death, which occurred during treatment period and follow-up period was 2.3% (7/304). Serious adverse events other than death were infectious mononucleosis, gastroenteritis, contusion, diabetes mellitus, intervertebral disc protrusion, colon cancer, and sleep apnoea syndrome in 1 subject for each. Of these, infectious mononucleosis, intervertebral disc

protrusion, and colon cancer were severe adverse events. The outcome was recovery for all except sleep apnoea syndrome.

The incidence rate of adverse events which were observed during treatment period and follow-up period and required withdrawal of the clinical study was 4.6% (14/304). Adverse events which were observed in 2 or more subjects and required withdrawal of the clinical study were pregnancy, depression, and suicidal ideation (2 subjects each). Of these adverse events, pregnancy (2 subjects) and depression (1 subject) were severe. Also, outcomes were recovery for all events except for depression and suicidal ideation (1 subject each, the same subject). Moreover, outcomes for pregnancy (2 subjects) were abortion spontaneous and normal delivery.

Table 2.3-3 Adverse events observed at the incidence rate of ≥5% (Study 3350, during treatment period)

Adverse events	MD-120 (n=304)
Nasopharyngitis	113 (37.2)
Somnolence	35 (11.5)
Headache	32 (10.5)
Nausea	31 (10.2)
Diarrhoea	24 (7.9)
Dizziness	23 (7.6)
Abdominal pain upper	19 (6.3)
Weight increased	19 (6.3)
Back pain	17 (5.6)
Constipation	16 (5.3)

Percentage of subjects with adverse events (%)

2.3.1.4 Overseas Post-Marketing Safety Data

The overseas post-marketing safety data have suggested no safety concerns, which supports the safety profile that has already been assessed and indicates a favorable benefit-risk profile.

2.3.2 Summary of benefits

The following are main efficacy-related study results from 3 overseas placebo-controlled studies in which MD-120 50 mg/day or 100 mg/day were examined (Study 332-US, Study 333-EU, and Study 335-US) and a global clinical Phase III study in patients with MDD including Japanese patients (Study 3359-ww). See “MD-120 Investigator’s Brochure” for details about the efficacy-related study results from each of the studies and other clinical studies.

2.3.2.1 3 overseas Phase III placebo-controlled studies (Study 332-US, Study 333-EU, and Study 335-US)

The placebo, MD-120 50 mg/day, and MD-120 100 mg/day were administered for 8 weeks to patients with MDD (447, 483, and 615 patients, respectively, in Study 332-US, Study 333-EU, and Study 335-US). In Study 335-US, duloxetine 60 mg/day was also administered for 8 weeks.

2. Background information

In all these studies, the superiority of the MD-120 50 mg group or MD-120 100 mg group to the placebo group was verified for the primary endpoint, the amount of change in the total HAMD17 score (ITT, LOCF) from the baseline to Week 8 visit during treatment period (Table 2.3-4).

Furthermore, the difference in the amount of change in the total MADRS score (ITT, LOCF) from the baseline to Week 8 visit during treatment period, the secondary endpoint, between the MD-120 50 mg group or MD-120 100 mg group and the placebo group was taken to be statistically significant as is for the primary endpoint (Table 2.3-5).

Table 2.3-4 Amount of change in the total HAMD17 score in 3 overseas Phase III placebo-controlled studies

(Week 8 visit during treatment period, LOCF, ANCOVA)

Study code	Treatment period	Treatment groups	Number of subjects	Amount of change in HAMD17 from the baseline (Adjusted mean [SE])	Difference from the placebo group (Adjusted mean [95%CI])	P value
332-US	Week 8	Placebo	150	−9 53 [0.58]	-	-
		50 mg	150	−11.5 [0.58]	1.9 [0.3, 3.5]	0.018
		100 mg	147	−11.0 [0.59]	1 5 [-0.1, 3.1]	0.065
333-EU	Week 8	Placebo	161	−10.7 [0.61]	-	-
		50 mg	164	−13.2 [0.60]	2.5 [0 9, 4.1]	0.002
		100 mg	158	−13.7 [0.61]	3.0 [1.4, 4.7]	<0.001
335-US	Week 8	Placebo	160	−8.68 [0.58]	-	-
		50 mg	148	−9.75 [0.60]	1 1 [-0.6, 2.7]	0.198
		100 mg	150	−10.50 [0.60]	1.8 [0.2, 3.4]	0.028
		Duloxetine 60 mg	157	−10.30 [0.60]	1.7 [0.0, 3.4]	0.047

Table 2.3-5 Amount of change in the total MADRS score in 3 overseas Phase III placebo-controlled studies

(Week 8 visit during treatment period, LOCF, ANCOVA)

Study code	Treatment period	Treatment groups	Number of subjects	Amount of change in MADRS from the baseline (Adjusted mean [SE])	Difference from the placebo group (Adjusted mean [95%CI])	P value
332-US	Week 8	Placebo	150	−12 3 [0.85]	-	-
		50 mg	148	−15.0 [0.85]	2.7 [0.4, 5.0]	0.022
		100 mg	142	−14 3 [0.87]	2.0 [−0.3, 4.4]	0.095
333-EU	Week 8	Placebo	161	−13 3 [0.79]	-	-
		50 mg	164	−16.4 [0.78]	3.1 [1.0, 5.2]	0.004
		100 mg	157	−17 5 [0.79]	4.2 [2.1, 6.3]	<0.001
335-US	Week 8	Placebo	156	−11.0 [0.82]	-	-
		50 mg	143	−12.7 [0.85]	1.7 [−0.6, 4.0]	0.149
		100 mg	145	−14.4 [0.84]	3.3 [1.1, 5.6]	0.004
		Duloxetine 60 mg	152	−14.4 [0.87]	3.4 [1.1, 5.8]	0.005

2.3.2.2 Global clinical Phase III study (Study 3359-ww)

The placebo, MD-120 25 mg/day, and MD-120 50 mg/day were administered for 8 weeks after 10 days of placebo run-in period to 699 patients with MDD including Japanese patients.

Although it was impossible to verify the superiority of the MD-120 25 mg group to the placebo group, the superiority of the MD-120 50 mg group to the placebo group was verified for the primary endpoint, the amount of change in the total HAMD17 score (ITT, LOCF) from the baseline to Week 8 visit during treatment period (ANCOVA, p=0.016) (Table 2.3-6).

Furthermore, the difference in the amount of change in the total MADRS score (ITT, LOCF) from the baseline to Week 8 visit during treatment period, the secondary endpoint, between only the MD-120 50 mg group and the placebo group was taken to be statistically significant as is for the primary endpoint (ANCOVA, p=0.016) (Table 2.3-7).

[redacted]

Table 2.3-6 Amount of change in the total HAMD17 score in Study 3359-ww
(Week 8 visit during treatment period, LOCF, Analysis of covariance)

Treatment period	Treatment groups	Number of subjects	Amount of change in HAMD17 from the baseline (Adjusted mean [SE])	Difference from the placebo group (Adjusted mean [95%CI])	P value
Week 8	Placebo	231	−8.52 [0.44]	-	-
	25 mg	232	−8.98 [0.44]	0.47 [−0.75, 1.69]	0.452
	50 mg	236	−10.02 [0.44]	1.50 [0.28, 2.72]	0.016

Table 2.3-7 Amount of change in the total MADRS score in Study 3359-ww
(Week 8 visit during treatment period, LOCF, Analysis of covariance)

Treatment period	Treatment groups	Number of subjects	Amount of change in MADRS from the baseline (Adjusted mean [SE])	Difference from the placebo group (Adjusted mean [95%CI])	P value
Week 8	Placebo	229	−9.23 [0.61]	-	-
	25 mg	231	−10.23 [0.60]	1.00 [−0.68, 2.68]	0.242
	50 mg	235	−11.29 [0.60]	2.06 [0.39, 3.73]	0.016

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]

2.3.3 Efficacy and Safety in the Elderly

In an overseas clinical pharmacology study in 48 healthy adults aged ≥18 years (Study 175-US) where a single dose of MD-120 was administered (at 300 mg to the first 10 subjects and at 200 mg to the remaining 38 subjects), the pharmacokinetics of MD-120 was not significantly different between the elderly (aged ≥65 years, 32 subjects) and non-elderly subjects (aged 18 and 45 years, 16 subjects). The overseas package insert describes that patients aged ≥65 years who had received MD-120 developed orthostatic systolic hypotension more often than patients aged <65 years; however, it also states that the efficacy and safety profile are not generally different between patients aged ≥65 years and patients aged <65 years[7)]. Furthermore, it specifies that the dose in the elderly should be determined in consideration to the possibility of decreased renal clearance. However, dose adjustment only according to the age is not required[7)].

3. Study design

3.1 Study type

3.1.1 Study type

Confirmatory study

3.1.2 Study design

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

3.2 Anticipated period of study participation

The anticipated period of participation in this clinical study will commence at informed consent and end at completion of follow-up period (Fig. 3.2-1, Table 3.2-1).

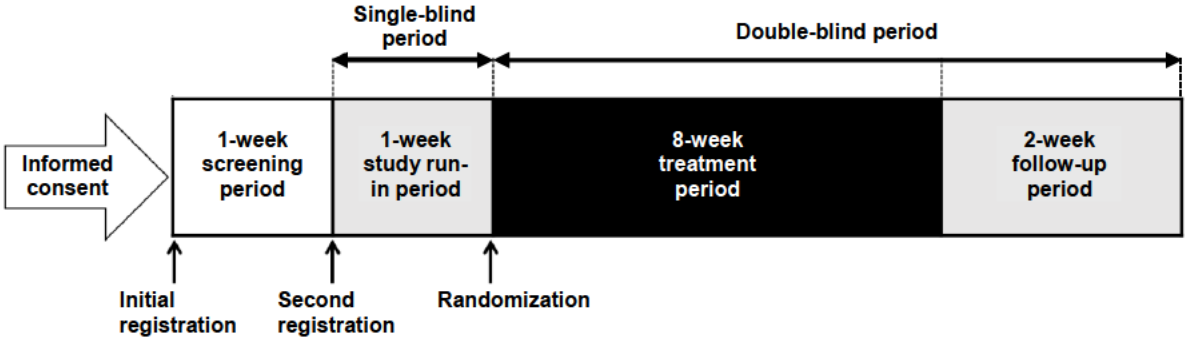


Figure 3.2-1 Anticipated period of study participation

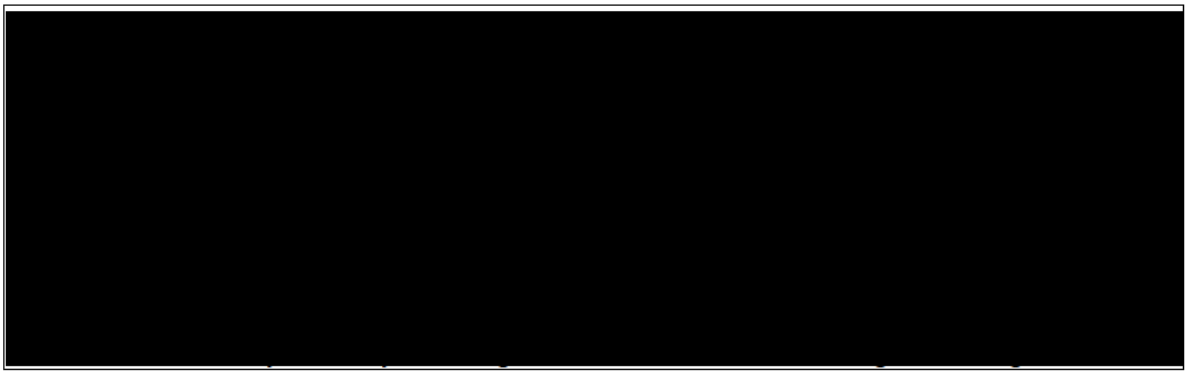
Table 3.2-1 Study participation period in each stage

Stage	Period	Administration of the investigational drug	Explanation
Screening period	1 week	Not administered	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	1 week	Administered	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	8 weeks	Administered	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	2 weeks	Administered	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.

3. Study design



3.3 Treatment groups

The subjects were randomly assigned to any of the following three groups.

(1) Placebo group

(2) MD-120 50 mg group

(3) MD-120 100 mg group

3.4 Dosage and administration

3.4.1 Administration

Once-daily oral administration. There is no specification about the time band for administration (See "7.2.1 Dose compliance of investigational drug").

The subjects will receive the first dose on the next day of the second registration or thereafter in run-in period, on the next day of randomization or thereafter in treatment period, and on the next day of the Week 8 visit during treatment period or the visit at the time of premature termination or thereafter in follow-up period.

3.4.2 Dosage

The administration schedule and the dose of investigational drug for each treatment group are as shown below (Figure 3.4-1).

	Run-in period (1 week)	Treatment period (8 weeks)		Follow-up period (2 weeks)
		Week 1 visit		Week 1 visit
Placebo	Placebo	Placebo		Placebo
MD-120 50 mg	Placebo	MD-120 50 mg/day		Placebo
MD-120 100 mg	Placebo	MD-120 50 mg/day	MD-120 100 mg/day	MD-120 50 mg/day

Figure 3.4-1 The administration schedule for each treatment group

(1) Run-in period

All subjects will receive the placebo (2 placebo tablets) from the start to the end of run-in period.

(2) Treatment period

[Placebo group]

- The subjects will receive the placebo (2 placebo tablets) from the start to the end of treatment period.

[MD-120 50 mg group]

- The subjects will receive MD-120 50 mg (1 MD-120 50 mg tablet) and the placebo (1 placebo tablet) from the start to the end of treatment period.

[MD-120 100 mg group]

- The subjects will receive MD-120 50 mg (1 MD-120 50 mg tablet) and the placebo (1 placebo tablet) from the start to Week 1 visit during treatment period.
- The subjects will receive MD-120 100 mg (2 MD-120 50 mg tablet) from the day following the Week 1 visit during treatment period to the end of treatment period.

(3) Follow-up period

[Placebo group]

- The subjects will receive the placebo (2 placebo tablets) from the start to Week 1 visit during follow-up period.

[MD-120 50 mg group]

- The subjects will receive the placebo (2 placebo tablets) from the start to Week 1 visit during follow-up period.

[MD-120 100 mg group]

- The subjects will receive MD-120 50 mg (1 MD-120 50 mg tablet) and the placebo (1 placebo tablet) from the start to Week 1 visit during follow-up period.

3. Study design

[redacted]

3.5 Endpoints

3.5.1 Primary endpoint

(1) Efficacy evaluation

Change in total MADRS score from baseline to Week 8 visit during treatment period

(2) Safety evaluation

Adverse events during treatment period and follow-up period

[Rationale for the design]

(1) Efficacy evaluation

The Clinical Evaluation Guideline recommends to use HAMD or MADRS as the main endpoints[12]. There is a correlation between the evaluations based on HAMD and MADRS, but MADRS is prepared to be more sensitive to the change in the severity of depression. Unlike HAMD, MADRS, which enables the unidimensional evaluation of psychiatric symptoms eliminating the impact of somatic symptoms, is considered to more correctly determine antidepressant effects in the comparison of the efficacy of antidepressants[13]. There was significant difference in the amount of change in the total MADRS score (ITT, LOCF) from the baseline to Week 8, between the MD-120 50 mg/day group and the placebo group as is for the primary endpoint (the amount of change in the total HAMD17 score from the baseline to Week 8) in Study 3359-ww in which all population including the Japanese population that use MADRS as the secondary endpoint (See "2.3.2 Summary of benefits").

It has been concluded, based on these reasons, that MADRS is appropriate as the primary endpoint for efficacy evaluation in this clinical study.

(2) Safety evaluation

Since collecting safety information during and after the administration of MD-120 in patients with depression is one of the purposes of this clinical study, adverse events during treatment period and follow-up period were determined as the endpoints.

3.5.2 Secondary endpoint

(1) Efficacy evaluation

1) Response evaluated by total MADRS score at Week 8 visit during treatment period
(Criteria for response: “Total MADRS score at Week 8 visit during treatment period is ≤50% of baseline score.”)
2) Remission evaluated by total MADRS score at Week 8 visit during treatment period
(Criteria for remission: “Total MADRS score at Week 8 visit during treatment period is ≤10.”)
3) Change in total HAMD17 score from baseline to Week 8 visit during treatment period
4) Response evaluated by total HAMD17 score at Week 8 visit during treatment period
(Criteria for response: “Total HAMD17 score at Week 8 visit during treatment period is ≤50% of baseline score.”)
5) Remission evaluated by total HAMD17 score at Week 8 visit during treatment period
(Criteria for remission: “Total HAMD17 score at Week 8 visit during treatment period is ≤7.”)
6) CGI-I at Week 8 visit during treatment period
7) Response evaluated by CGI-I at Week 8 visit during treatment period
(Criteria for response: “Evaluated as “1. Very much improved” or “2. Much improved” at Week 8 visit during treatment period”)
8) Change in CGI-S from baseline to Week 8 visit during treatment period
9) Change in total $QIDS_{16}$-SR-J score from baseline to Week 8 visit during treatment period
10) Change in total SDS score from baseline to Week 8 visit during treatment period

(2) Safety evaluation
1) ADRs during treatment period and follow-up period
2) Adverse events and ADRs during treatment period
3) Adverse events and ADRs during follow-up period

4. Inclusion and exclusion criteria of subjects

4.1 Target

Patients with depression

4.2 Inclusion and exclusion criteria

4.2.1 Initial registration

4.2.1.1 Inclusion criteria

At the initial registration, patients meeting all of the following inclusion criteria will be included in this clinical study.

(1) Patients who have consented in writing to participate in this clinical study
(2) Outpatients aged ≥20 years at the time of informed consent
(3) Patients with "depression" who have experienced non-psychotic or non-mixed single or repeated episode, which has been diagnosed according to DSM-5 (for DSM-5-based diagnosis, Mini-International Neuropsychiatric Interview [M.I.N.I.] version 7.0.2 will be used as a diagnostic aid tool)
(4) Patients in whom the current depressive episode has persisted for ≥3 months and ≤18 months if it is single or for ≥1 months and ≤18 months if it is recurrent, according to DSM-5
(5) Patients with the total score of ≥20 in Hamilton Depression Rating Scale (HAMD) 17 and the sub-score of ≥2 for Item 1 (depressed mood)
(6) Patients with the score of ≥4 in CGI-S
(7) Patients with the total score of ≥16 in Quick Inventory of Depressive Symptomatology $(QIDS)_{16}$-SR-J

[Rationale for the establishment]
(1) It was established as the basic matter for the clinical study.
(2) The lower age limit of 20 years was established in consideration of ability in making decision of consent.
(3) For diagnosis of depression based on standardized criteria, the sponsor selected DSM-5, which is generally used as diagnostic criteria for mental disorder. To support diagnosis using DSM-5, M.I.N.I., a structured interview form for mental disorder, was selected as a tool for diagnostic aid.
(4) It was established to ensure appropriate efficacy and safety evaluation of MD-120 in patients with depression.
(5) - (7) In light of the criteria in Study 3359-ww, 3 overseas placebo-controlled studies, and clinical studies of the other antidepressant drugs, it was established to select patients with moderate or severe depression in this clinical study, which is intended to appropriately evaluate the efficacy of MD-120 for treatment of depression.

4.2.1.2 Exclusion criteria

At the initial registration, individuals who meet any of the following exclusion criteria will be excluded from this clinical study.

(1) Patients judged by the (sub-)investigator to have any of the following disorders classified according to DSM-5 (using a diagnostic aid tool of M.I.N.I. version 7.0.2 if appropriate)
- Intellectual disabilities
- Autism spectrum syndrome/Autism spectrum disorder
- Attention deficit and hyperkinesia/Attention deficit and hyperactivity disorder
- Schizophrenia spectrum disorder and other psychotic disorders
- Bipolar and related disorders
- Obsessive disorder syndrome and related syndromes/Obsessive compulsive disorder and related disorders
- Psychic trauma and stress-related disorders
- Disassociation syndrome/dissociative disorders
- Eating behavior disorders and eating disorders
- Substance-related disorders (except for those caused by tobacco or caffeine)
- Neurocognitive deficiency
- Personality disorders

(2) Patients concurrently with any of the following disorders classified according to DSM-5, which is also positioned as the main disorder by the (sub-)investigator (using a diagnostic aid tool of M.I.N.I. version 7.0.2 if appropriate)
- Anxiety/Anxiety disorders

(3) Patients judged by the (sub-)investigator to have a past history of any of the following disorder classified according to DSM-5 (using a diagnostic aid tool of M.I.N.I. version 7.0.2 if appropriate)
- Schizophrenia spectrum disorder and other psychotic disorders
- Bipolar and related disorders
- Substance-related disorders (except for those caused by tobacco or caffeine)

(4) Patients meeting any of the followings:
- Patients who presented a certain form of followings “suicidal behavior” (suicide attempt, interrupted suicide attempt, withdrawn suicide attempt, and preparatory behavior) within 1 year before the start of the screening period as assessed according to Columbia-Suicide Severity Rating Scale (C-SSRS)
- Patients meeting any of B14 or B16 under “B. Suicidal ideation, Self-injurious and Suicidal behavior” or B18 within past 12 months in M.I.N.I. version 7.0.2
- Patients with the sub-score of ≥3 for Item 11 (suicide) in HAMD17
- Patients with the sub-score of ≥5 for Item 10 (Thought of Death or Suicide) in Montgomery-Asberg Depression Scale (MADRS)
- Patients with the sub-score of ≥3 for Item 12 (Suicidal ideation) in $QIDS_{16}$-SR-J
- Patients judged by the (sub-)investigator to be at a high risk of suicide

(5) Patients who have a first-degree relative (parent, sibling, and child) with bipolar and related disorders

4. Inclusion and exclusion criteria of subjects

(6) Patients with a past history of or co-existing convulsive disorder such as epilepsy (excluding fever seizure)
(7) Patients with a past history of or co-existing acute angle closure glaucoma or elevated intraocular pressure
(8) Patients who have received desvenlafaxine
(9) Patients who received venlafaxine for the current depressive episode
(10) Patients with serious drug allergy or hypersensitivity, or hypersensitivity to venlafaxine or desvenlafaxine
(11) Patients who received other investigational drugs within 16 weeks before the start of the screening period
(12) Patients who received but were not responsive to two or more antidepressants given at an adequate dose (in the range of approved dose excluding initial low dose, and doctors who treat the patients judged to be adequate) for at least 4 weeks for the current or past depressive episode
(13) Patients who have undergone electroconvulsive therapy or transcranial magnetic stimulation (TMS) therapy
(14) Patients with a history of hospitalization owing to psychiatric disorder excluding depression
(15) Patients who received any antipsychotics within 2 weeks before the start of the screening period (or within 6 months for a depot formulation)
(16) Patients who received a hypnotic/sedative (excluding zopiclone, zolpidem, and eszopiclone) within 2 weeks before the start of the screening period
(17) Patients with a co-existing serious hepatic, renal, hematological, respiratory, gastrointestinal, or cardiovascular disease, or metabolism/electrolytes abnormality
(18) Female patients who are or may be pregnant, are breast-feeding, or male and female patients who are intend to conceive during the study period
(19) Patients who are otherwise judged by the (sub-) investigator to be ineligible for this clinical study

[Rationale for the design]
(1) - (3) These items were established, because these may affect appropriate evaluation of the efficacy and safety of MD-120 in patients with depression.
(4) It was established to ensure the safety of subjects.
(5) It was established, because the subject potentially has a bipolar disorder owing to such genetic background, which may affect appropriate evaluation of the efficacy and safety.
(6) - (7) It was established to ensure the safety of subjects, because overseas package insert recommends that “should use cautiously” or “should avoid using” for these disorders and symptoms in “WARNING AND PRECAUTIONS”.
(8) - (9) These items were established, because these may affect appropriate evaluation of the efficacy and safety of MD-120.
(10) It was established to ensure the safety of subjects.
(11) It was established as the basic matter for the clinical study.

(12) It was established, because patients resistant to antidepressant drugs may not be appropriately evaluated for the efficacy and safety of MD-120 for depression treatment.
(13) - (14) These items were established, because such subjects may concurrently have a severe psychiatric disorder other than depression, and thus may not be appropriately evaluated for the efficacy and safety of MD-120 for depression treatment.
(15) - (16) These items were established, because these may affect appropriate evaluation of the efficacy and safety of MD-120.
(17) It was established to ensure the safety of subjects.
(18) It was established to ensure the safety of subjects and partner of male subjects.
(19) It was established as the basic matter for the clinical study.

4.2.2 Second registration

4.2.2.1 Inclusion criteria

At the second registration, subjects meeting all of the following inclusion criteria will be included in this clinical study.

(1) Patients in whom the depressive episode at the time of the initial registration persists
(2) Patients with the total score of ≥20 in Hamilton Depression Rating Scale (HAMD) 17 and the sub-score of ≥2 for Item 1 (depressed mood)
(3) Patients with the score of ≥4 in CGI-S
(4) Patients with the total score of ≥16 in Quick Inventory of Depressive Symptomatology (QIDS)$_{16}$-SR-J

[Rationale for the design]
The above criteria were established as explained in [Rationale for the establishment] for "4.2.1.1 Inclusion criteria (initial registration)."

4.2.2.2 Exclusion criteria

At the second registration, subjects who meet any of the following exclusion criteria will be excluded from this clinical study.

(1) Patients meeting any of the followings:
    - Patients who presented a certain form of followings "suicidal behavior" (suicide attempt, interrupted suicide attempt, withdrawn suicide attempt, and preparatory behavior) between the initial and second registrations as assessed according to C-SSRS
    - Patients with the sub-score of ≥3 for Item 11 (suicide) in HAMD17
    - Patients with the sub-score of ≥5 for Item 10 (Suicidal Thoughts) in Montgomery-Asberg Depression Scale (MADRS)
    - Patients with the sub-score of ≥3 for Item 12 (Thought of Death or Suicide) in QIDS$_{16}$-SR-J
    - Patients judged by the (sub-)investigator to be at a high risk of suicide
(2) Patients who received a drug or therapy prohibited for concomitant use from the start of screening period

4. Inclusion and exclusion criteria of subjects

(3) Patients who deviated from the conditions for concomitant use of hypnotics/sedatives allowed for use from the start of screening period

(4) Patients determined by the (sub-)investigator to be ineligible for the study based on the result of diagnosis confirmation by the Clinical data analytics committee regarding the assessment at the time of the initial registration by the (sub-)investigator for the diagnosis

(5) Patients who are otherwise not eligible for this clinical study as determined by the (sub-)investigator

[Rationale for the design]

(1) It was established to ensure the safety of subjects.

(2) It was established, because these may affect appropriate evaluation of the efficacy and safety of MD-120 in patients with depression and to ensure the safety of subjects.

(3) These items were established because subjects may deviate from the conditions for concomitant use of hypnotics/sedatives during treatment period, and also the items may affect appropriate evaluation of the efficacy and safety of MD-120.

(4) This item was set out since subjects thereto applicable would not be appropriate for the efficacy and safety evaluation of MD-120.

(5) It was established as the basic matter for the clinical study.

4.2.3 Randomization registration

4.2.3.1 Inclusion criteria

At the randomization registration, subjects meeting all of the following inclusion criteria will be included in this clinical study.

(1) Patients in whom the depressive episode at the time of the initial registration persists

(2) Patients with the total score of ≥20 in Hamilton Depression Rating Scale (HAMD) 17 and the sub-score of ≥2 for Item 1 (depressed mood)

(3) Patients with the score of ≥4 in CGI-S

(4) Patients with the total score of ≥16 in Quick Inventory of Depressive Symptomatology (QIDS)$_{16}$-SR-J

[Rationale for the design]

The above criteria were established as explained in [Rationale for the establishment] for "4.2.1.1 Inclusion criteria (initial registration)."

4.2.3.2 Exclusion criteria

At the randomization registration, subjects who meet any of the following exclusion criteria will be excluded from this clinical study.

(1) Patients meeting any of the followings:

- Patients who presented a certain form of followings "suicidal behavior" (suicide attempt, interrupted suicide attempt, withdrawn suicide attempt, and preparatory behavior) between the second registration and randomization as assessed according to C-SSRS

- Patients with the sub-score of ≥3 for Item 11 (suicide) in HAMD17
- Patients with the sub-score of ≥5 for Item 10 (Suicidal Thoughts) in MADRS
- Patients with the sub-score of ≥3 for Item 12 (Thought of Death or Suicide) in $QIDS_{16}$-SR-J
- Patients judged by the (sub-)investigator to be at a high risk of suicide

(2) Patients whose total score in HAMD17 deteriorated or improved by ≥25% from the second registration

(3) Patients who missed taking the investigational drug on ≥2 days during run-in period

(4) Patients who have received a concomitant drug or therapy prohibited from the start of screening period

(5) Patients who deviated from the conditions for concomitant use of hypnotics/sedatives allowed for use from the start of screening period

(6) Patients determined by the (sub-)investigator to be ineligible for the study based on the result of diagnosis confirmation by the Clinical data analytics committee regarding the assessment at the time of the initial registration by the (sub-)investigator for the diagnosis

(7) Patients who are otherwise judged by the (sub-) investigator to be ineligible for this clinical study

[Rationale for the design]

(1) It was established to ensure the safety of subjects.

(2) It was established, because subjects who have responded to the placebo or marked exacerbation of symptoms during the period are not appropriate for the efficacy and safety evaluation of MD-120.

(3) It was established, because subjects who have failed compliance during such period can not be expected to keep the compliance during treatment and subsequent periods, interfering with appropriate evaluation of the efficacy and safety of MD-120.

(4) It was established, because these may affect appropriate evaluation of the efficacy and safety of MD-120 in patients with depression and to ensure the safety of subjects.

(5) These items were established, because they may also be deviated during treatment period, or affect the appropriate evaluation of the efficacy and safety of MD-120.

(6) This item was set out since subjects thereto applicable would not be appropriate for the efficacy and safety evaluation of MD-120.

(7) It was established as the basic matter for the clinical study..

5. Clinical study procedures

5.1 Informed consent

5.1.1 Preparation of informed consent form and written patient information

The investigator will prepare an informed consent form used to obtain patient's consent to participation in the clinical study based on "Written patient information for trials of MD-120 (draft)" provided by the sponsor. The written patient information shall include matters specified in the Good Clinical Practice (GCP). The investigator will submit the prepared written patient information to the head of the study center, obtain the approval from the institutional review board, and then submit the approved document to the sponsor.

5.1.2 Selection of subjects, explanation of the clinical study with written information, and obtaining informed consent

(1) The (sub-)investigator will give a patient the written patient information and explain the content to him or her before the start of the clinical study.

(2) After confirming that the patient has understood the content of the written patient information, the (sub-)investigator will obtain the voluntary consent to participation in the clinical study from the patient.

(3) The (sub-)investigator and patient will sign the informed consent and enter the respective dates. The clinical research coordinator will also sign it and enter the respective date if he or she has given supplementary explanation.

(4) The patient will be defined as a subject by signing the informed consent and entering the respective date.

(5) The (sub-)investigator will retain the original copy of the signed written informed consent in a duplicate form with the original medical records (medical charts, etc.) and deliver the duplicate copy to the subject.

(6) The (sub-)investigator will record the concerned delivery of the written patient information and the duplicate copy of the written informed consent.

5.1.3 Information provision after informed consent

(1) If the sponsor provides new information that may affect the subject's willingness to continue participation in the clinical study, the (sub-)investigator will promptly convey that information to the subject, check whether he or she wishes to continue participation in the clinical study again, and record practice and result of the check in the original medical record.

(2) The investigator will promptly revise the written patient information when recognizing such necessity. The investigator will submit the revised written patient information to the head of the

study center, obtain the approval from the institutional review board, and then submit the approved document to the sponsor.

(3) Upon revision of the written patient information, the (sub-)investigator will give explanation again using the revised written patient information in accordance with "5.1.2 Selection of subjects, explanation of the clinical study with written information, and obtaining informed consent." In addition, the (sub-)investigator will obtain voluntary written re-consent to continued participation in the clinical study from the subject.

5.2 Observation and test, and evaluation schedule

Table 5.2-1 shows the observation and test, Table 5.2-2 shows planned day for visits and acceptable window, and Table 5.2-3 shows evaluation schedule as well as details of the general laboratory test and vital signs.

5. Clinical study procedures

Table 5.2-1 Observation and test, and evaluation schedule

		Screening period (1 week)			Single-blind period: Run-in period (1 week)		Double-blind period: Treatment period (8 weeks)						Follow-up period (2 weeks)	
		Initial registration: Start		Second registration: End	Start	End or premature termination	Randomization: Start	Week 1	Week 2	Week 4	Week 6	Week 8 or premature termination	Week 1 or premature termination[a]	End or premature termination[b]
Visit (N)		1		2	-	3	-	4	5	6	7	8	9	10
Informed consent	✓													
Inclusion and exclusion criteria		✓		✓		✓[g]								
Subject baseline characteristics[c]		✓												
M.I.N.I.		✓												
DSM-5 (Diagnosis of depression)		✓												
Diagnosis confirmation		✓												
MADRS		✓		✓		✓[g]		✓	✓	✓	✓	✓		
HAMD17		✓		✓		✓[g]			✓	✓		✓		
CGI-S		✓		✓		✓[g]		✓	✓	✓	✓	✓		
CGI-I								✓	✓	✓	✓	✓		
$QIDS_{16}$-SR-J		✓		✓		✓[g]		✓	✓	✓	✓	✓		
SDS		✓				✓[g]				✓		✓		
C-SSRS		✓		✓		✓[g]		✓	✓	✓	✓	✓	✓	
Vital signs and body weight		✓		✓		✓[g]		✓	✓	✓	✓	✓	✓	
Body height[d]		✓												
Drug concentration measurement									✓	✓		✓		
General laboratory test			✓[f]						✓	✓		✓		
Pregnancy test[e]		✓												
Standard 12-lead ECG		✓				✓[g]						✓		
Concomitant therapies		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adverse events					✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Dispensing and retrieval of investigational drug				✓		✓		✓	✓	✓	✓	✓	✓	

a: The time of premature termination before Week 1 during follow-up period.
b: The time of premature termination after Week 1 during follow-up period.
c: Subject baseline characteristics: Gender, race, date of birth, date of informed consent, height, time of the initial depression onset, frequency of depressive episodes, the start time of the current depressive episode, the applicability of the DSM-5 criteria to each depressive symptom, a history of treatment with antidepressant drugs (chemical names)

for the current and past depressive episodes, a history of treatment with hypnotics/sedatives and (chemical names), and a history of treatment with antianxiety drug (presence/absence) (See "13.1 Subject baseline characteristics").
d: Included in "Subject baseline characteristics".
e: Performed only for premenopausal female subjects.
f: The urinalysis is allowed to be performed before the initial registration as a non-invasive test.
g: Not performed at the time of premature termination

Table 5.2-2 Planned day for visits and acceptable window

Visit	Planned day	Planned day (acceptable window)
1	Start of screening period	-
2	End of screening period	Day 8 (+3) starting from the day of visit that is Day 1.
-	Start of run-in period (no visit)	The next day of the second registration
3	End of run-in period or the time of premature termination	Day 7 (±1) starting from the start of run-in period that is Day 1.
-	Start of treatment period (no visit)	The next day of randomization
4	Week 1 visit during treatment period	Day 7 (±1) starting from the start of treatment period that is Day 1
5	Week 2 visit during treatment period	Day 14 (±3) starting from the start of treatment period that is Day 1
6	Week 4 visit during treatment period	Day 28 (±3) starting from the start of treatment period that is Day 1
7	Week 6 visit during treatment period	Day 42 (±3) starting from the start of treatment period that is Day 1
8	Week 8 visit during treatment period or the time of premature termination	Day 56 (±3) starting from the start of treatment period that is Day 1
9	Week 1 visit during follow-up period or the time of premature termination	Day 7 (±1) starting from the next day of the Week 8 visit during treatment period or the visit at premature termination that is Day 1
10	End of follow-up period or the time of premature termination	Day 7 (+7) starting from the next day of the Week 1 visit during follow-up period or the visit at premature termination that is Day 1

Table 5.2-3 General laboratory test and vital signs

Test		Test items
General laboratory test	Hematology	White blood cell count (WBC), red blood cell count (RBC), hemoglobin, hematocrit, and platelet count
	Blood biochemistry	AST (GOT), ALT (GPT), ALP, gamma-GTP, total bilirubin, total protein, albumin, urea nitrogen, creatinine, total cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol, blood glucose, HbA1c, sodium, potassium, and chloride
	Urinalysis (qualitative)	Urine protein, urine glucose, and occult blood in urine
Vital signs		Sitting blood pressures (systolic/diastolic), and pulse rates

5.2.1 Initial registration

The (sub-)investigator will perform observation, tests and evaluation necessary for eligibility assessment on the patient with the written informed consent in accordance with “Table 5.2-1 Observation and test, and evaluation schedule” and proceed with the initial registration in accordance with the procedure as shown in Table 5.2-4.

Table 5.2-4 Procedure and description of the initial registration

Procedure	Description
Eligibility assessment ↓	• Inspect if the patient meets each of the inclusion criteria and exclusion criteria for the initial registration • Assess the eligibility for the initial registration
Application of the initial registration ↓	• Enter required information in the subject registration system, and apply case registration to the subject registration center
Result of the initial registration ↓	• Check the eligibility assessment result provided by the subject registration center
Notifying subject of the registration result ↓	• If the subject registration center provides an “eligible” result to the subject in the eligibility assessment, notify him or her of that matter. • If the subject registration center provides an “ineligible” result to the subject in the eligibility assessment, notify him or her of that matter and terminate the clinical study for him or her.
Continuation of clinical study	• Perform general clinical laboratory tests as scheduled at the start of screening period. • Schedule the next visit with the subject • Hand the drug-use diary.

5.2.2 Second registration

The (sub-)investigator will perform observation, tests, and evaluation in accordance with “Table 5.2-1 Observation and test, and evaluation schedule.” The (sub-)investigator will proceed with the second registration in accordance with the procedure as shown in Table 5.2-5 and dispense the investigational drug to eligible subjects.

When a subject meets “8.1.1 Withdrawal criteria in the screening period and run-in period,“ the (sub-)investigator will withdraw him or her from the clinical study in accordance with the procedure as shown in “8.2-1 Withdrawal in screening period.”

Table 5.2-5 Procedure and description of the second registration

Procedure	Description
Observation and evaluation at the end of screening period ↓	• Inspect if the subject meets each of the inclusion criteria and exclusion criteria for the second registration • Assess the eligibility for the second registration

Application of the second registration ↓	• Enter required information in the subject registration system, and apply case registration to the subject registration center
Result of the second registration ↓	• Check the eligibility assessment result provided by the subject registration center
Notifying subject of the registration result ↓	• If the subject registration center provides an “eligible” result to the subject in the eligibility assessment, notify him or her of that matter. • If the subject registration center provides an “ineligible” result to the subject in the eligibility assessment, notify him or her of that matter and terminate the clinical study for him or her.
Continuation of clinical study	• Schedule the next visit with the subject • Dispense the investigational drug

5.2.3 Randomization registration

The (sub-)investigator will perform observation, tests, and evaluation in accordance with “Table 5.2-1 Observation and test, and evaluation schedule.” The (sub-)investigator will proceed with the randomization registration in accordance with the procedure as shown in Table 5.2-6 and dispense the investigational drug to eligible subjects.

When a subject meets “8.1.1 Withdrawal criteria in the screening period and run-in period,“ the (sub-)investigator will withdraw him or her from the clinical study in accordance with the procedure as shown in “8.2-2 Withdrawal in run-in period.”

Table 5.2-6 Procedure and description of the randomization registration

Procedure	Description
Observation and evaluation at the end of run-in period ↓	• Inspect if the subject meets each of the inclusion criteria and exclusion criteria for the randomization registration • Assess the eligibility for the randomization registration
Application of the randomization registration ↓	• Enter required information in the subject registration system, and apply randomization registration to the subject registration center
Result of the randomization registration ↓	• Check the eligibility assessment result provided by the subject registration center
Notifying subject of the registration result ↓	• If the subject registration center provides an “eligible” result to the subject in the eligibility assessment, notify him or her of that matter. • If the subject registration center provides an “ineligible” result to the subject in the eligibility assessment, notify him or her of that matter and terminate the clinical study for him or her.
Continuation of clinical study	• Schedule the next visit with the subject • Dispense the investigational drug

5.2.4 Treatment period

The (sub-)investigator will perform observation, tests, and evaluation in accordance with “Table5.2-1 Observation and test, and evaluation schedule.” The (sub-)investigator will schedule the next visit and then dispense an appropriate amount of the investigational drug as needed until the next visit.

When a subject meets “8.1.2 Withdrawal criteria in the treatment period,“ the (sub-)investigator will take actions in accordance with “8.2 Withdrawal procedures for individual subjects.“

5.2.5 Follow-up period

The (sub-)investigator will perform observation, tests, and evaluation in accordance with “Table5.2-1 Observation and test, and evaluation schedule.”

When a subject meets “8.1.3 Withdrawal criteria in the follow-up period,“ the (sub-)investigator will take actions in accordance with the procedure as shown in “8.2-4 Withdrawal in follow-up period .“

6. Investigational drug

6.1 Dosage form and content of investigational drug

In this clinical study, the investigational drug described in Table 6.1-1 will be used.

Table 6.1-1 Dosage form, appearance ,and content of investigational drug

Investigational drug	Dosage form and appearance	Content
MD-120 50 mg tablet	Extended-release tablet: Pale red square-shaped film-coated tablet with a pyramidal shape on one side	Each tablet contains 50 mg of desvenlafaxine
Placebo tablet	Extended-release tablet: Pale red square-shaped film-coated tablet with a pyramidal shape on one side	No desvenlafaxine contained

6.2 Procedures for management of the investigational drug

The investigational drug storage manager will keep and retain the records on receipt of the investigational drug provided by the sponsor, its incoming and outgoing amounts at the pharmacy of the study center, use status for each subject, and return of the remaining investigational drug in accordance with “Written procedure for management of the investigational drug“ and “Written instructions for handling the investigational drug“ provided by the sponsor and written standard operation procedures at the study center.

6.3 Method for randomization and blinding

6.3.1 Blinding in run-in period

The (sub-)investigator shall not inform any subject that he or she is supposed to take the placebo during run-in period.

6.3.2 Randomization registration

The person responsible for investigational drug randomization will randomize the investigational drug by the permuted block method in which the study center is defined as a block in accordance with separately prepared “Written specifications for randomization. Subjects assessed to be eligible at the randomization registration will be randomly assigned to any of the three groups at a ratio of 1:1:1.

6.3.3 Maintenance of blindness

6.3.3.1 Handling of investigational drug randomization table

(1) After the end of the randomization, the person responsible for investigational drug randomization will separately seal the original copy and one duplicate copy of the following investigational drug randomization tables. The person responsible for investigational drug randomization and sponsor will retain the original copy and one duplicate copy, respectively, until unblinding after the completion of the clinical study. Also, the person responsible for the subject registration will incorporated the information in the investigational drug randomization table in the subject registration system which will be used for emergency unblinding described in section 6.4.1, and verification of treatment groups to which each subject has been randomized at the drug concentration measurement laboratory as described in section 6.3.3.2.

(2) Unblinding will be implemented in accordance with "6.4Procedure for unblinding with the investigational drug assignment table," where necessary.

(3) If the sponsor retrieves the investigational drug before unblinding, the investigational drug storage manager will check the quantity of the remainder of the investigational drug and seal the outer box. Unopened boxes, if any, will be retrieved without sealing.

6.3.3.2 Maintenance of unblindness at the drug concentration measurement laboratory

(1) In this study, blood sampling will be performed for all subjects randomized for the investigational drug; however, drug concentration measurement is performed only for the MD-120 groups (50 mg group and 100 mg group). Therefore, the drug concentration measurement laboratory will be unblinded since it needs to verify the treatment group to which each subject will be randomized pertinent to measurement of drug concentration. The person responsible for the subject registration will provide the drug concentration measurement laboratory with an unblineded accecc to the subject registration system. The drug concentration measurement laboratory will verify the treatment group on the subject registration system in accordance with the procedures separately prepared by the drug concentration measurement laboratory. The information concerning the unblinded accounts and treatment groups should be handled appropriately in accordance with the procedures.

(2) The drug concentration measurement laboratory will store the account of unblineded, the information of the treatment group and the measurement results properly in accordance with the procedures separately prepared.

6.4 Procedure for unblinding with the investigational drug assignment table

6.4.1 Unblinding with investigational drug assignment table for emergency unblinding during the study period

(1) The (sub-)investigator will promptly communicate with the sponsor and request the emergency unblinding if he or she considers it necessary to know of which group the investigational drug was administered (for instance, in the case where such unblinding is considered urgently necessary because actions have to be taken on a serious adverse event).

(2) Even in a case other than (1), the sponsor can decide emergency unblinding in consultation with the (sub-)investigator if they consider it necessary to know of which group the investigational drug was administered.

(3) For emergency unblinding described in (1) or (2), the sponsor will access the subject registration system and unblind the information for each subject in accordance with the "Written procedure for unblinding with investigational drug assignment table for emergency unblinding" separately prepared by the sponsor.

(4) The sponsor will provide the investigational drug randomization information to the concerned (sub-)investigator.

(5) If measurements of drug concentration are required pertinent to an emergency unblinding, the sponsor will notify the drug concentration measurement laboratory and request the measurements of drug concentration on the subject, and in turn, the drug concentration measurement laboratory will submit to the sponsor the measurements of drug concentration on the subject in accordance with the procedures separately prepared.

6.4.2 Unblinding after lock of database

6.4.2.1 Lock of database

After the end of the follow-up period for all the subjects, the sponsor will determine handling of the data in all the subjects in analyses as specified in this study protocol (See "15.2 Analysis sets") and lock the database. For the above determination, advices from medical experts may be sought where necessary.

6.4.2.2 Unblinding

Unblinding shall be performed in accordance with separately prepared "Written procedure for investigational drug randomization."

7. Treatment and instructions for subjects

7.1 Prohibited and allowed therapies

7.1.1 Prohibited concomitant drugs

Table 7.1-1 shows prohibited concomitant treatment drugs in this clinical study (See "Annex 4 List of prohibited concomitant drugs"). If the prohibited concomitant treatment becomes unavoidable owing to exacerbation of the target disorder or adverse events, and the subject meets "8.1 Withdrawal criteria for individual subjects," he or she will be withdrawn from the clinical study in accordance with "8.2 Withdrawal procedures for individual subjects," and then appropriate treatment will be given.

Table 7.1-1 Prohibited concomitant drugs

Concomitant drugs prohibited from the start of screening period to the end of follow-up period
(1) MAO inhibitors*
(2) Investigational drugs other than MD-120
(3) Desvenlafaxine and venlafaxine other than MD-120
Concomitant drugs prohibited from the start of screening period to the completion of all observation and tests scheduled at the visit at the end of treatment period
(4) Antipsychotic drugs
(5) Antianxiety drugs
(6) Hypnotic/sedative drugs (excluding zopiclone, zolpidem, and eszopiclone)
(7) Hypnotic drugs
(8) Antidepressant drugs
(9) Antimanic drugs
(10) Antiepileptic drugs
(11) Antiparkinson drugs
(12) Chinese medicines indicated for treatment of anxiety, insomnia, and depressed mood
(13) Drugs containing serotonin precursor (L-tryptophan, 5-hydroxytryptophan, etc.)
(14) Drugs containing tramadol
(15) Triptan drugs

*If MAO inhibitors are administered after the end of treatment with MD-120, there must be an interval of at least 7 days.

[Rationale for the establishment of prohibited concomitant drugs]
(1) It was established to ensure the safety of subjects, because their concomitant use with MD-120 may lead to onset of serotonin syndrome.
(2) It was established as a basic requirement for a clinical trial.
(3) - (12) These items were established, because these are considered to affect appropriate evaluation of the efficacy and safety of MD-120.

(13) - (15) These items were established, because concomitant use of these drugs with MD-120 may enhance the serotonergic action, potentially affecting appropriate evaluation of the efficacy and safety of MD-120.

7.1.2 Prohibited concomitant therapies

Table7.1-2 shows prohibited concomitant therapies in this clinical study. If the prohibited concomitant therapy becomes unavoidable owing to exacerbation of the target disorder or adverse events, and the subject meets "8.1. Withdrawal criteria for individual subjects," he or she will be withdrawn from the clinical study in accordance with "8.2 Withdrawal procedures for individual subjects," and then appropriate treatment will be given.

Table7.1-2 Prohibited concomitant therapies

Concomitant therapies prohibited from the start of screening period to the end of follow-up period
(1) Electroconvulsive therapy
(2) Transcranial magnetic stimulation (TMS) therapy
(3) Supplement containing St. John 's Wort as the active ingredient
Concomitant therapies prohibited from the start of screening period to the completion of all observation and tests scheduled at the end of treatment period
(4) Systematized psychotherapies (including cognitive behavior therapies)

[Rationale for the establishment of prohibited concomitant therapies]
(1)-(4) These items were established, because these may affect appropriate evaluation of the efficacy and safety of MD-120.

7.1.3 Allowed concomitant drugs

Concomitant use of hypnotic/sedative drugs is allowed only when their use is as specified in (1) to (3). Table7.1-3 shows allowed concomitant hypnotic/sedative drugs. If the use of drugs that deviates from the regulations of allowed concomitant drugs becomes unavoidable owing to exacerbation of the target disease or adverse events, and the subject meets "8.1 Withdrawal criteria for individual subjects," he or she will be withdrawn from the clinical study in according with "8.2 Withdrawal procedures for individual subjects," and then appropriate treatment will be given.

(1) Concomitant use of the hypnotic/sedative drugs listed in Table 7.1-3 are allowed from the start of screening period to the completion of all observation and tests scheduled at the end of treatment period only for the subjects who were using these drugs as of 2 weeks before the start of the screening period.

7. Treatment and instructions for subjects

(2) During screening, run-in, and treatment period, use of only 1 drug is allowed as a single dose up to 3 days a week (use for up to 3 days per 7-day time frame starting from the start of screening period is allowed), but prohibited within 24 hours before visit specified in "Table 5.2-1 Observation and test, and evaluation schedule.".

(3) The maximum dose should be 7.5 mg/night for zopiclone, 5 mg/night for zolpidem, and 2 mg/night for eszopiclone.

After all the observations, tests, and evaluations at the end of treatment period are completed, the above (2) and (3) will not apply. Concomitant drugs may be used at the discretion of the (sub-)investigator.

Table7.1-3 Allowed concomitant hypnotic/sedative drugs

Allowed concomitant hypnotic/sedative drugs
(1) Zopiclone
(2) Zolpidem
(3) Eszopiclone

[Rationale for the establishment of allowed concomitant drugs]

To treat sleep disorder associated with depression, concomitant use of hypnotic/sedative drugs is allowed in ethical consideration of the subjects. To minimize an impact of the efficacy evaluation of MD-120, types of the drugs and regimens are restricted considering that the Clinical Assessment Guideline recommends to set out a rule to not change the dosage regimen of a psychotropics during clinical studies and also to limit the concomitant use of hypnotics/sedatives to those of super-short action since concomitant use of antianxiety, hypnotics/sedatives or mental treatment may affect the efficacy and safety assessments[12)].

7.2 Instructions for subjects

7.2.1 Dose compliance of investigational drug

The (sub-)investigator will verify subjects' dose compliance at each visit and instruct them on dose compliance, and also, at the time of the prescription, instruct subjects to:

(1) Administer the investigational drug according to the (sub-)investigator's instruction;

(2) Administer the investigational drug at around the same time every day whether with food or not, while the time of dose can be at any time;

(3) Not bite on, crack, or crush the investigational drug, and administer it without any modification;

(4) Administer the investigational drug before the following visits; the visit of the end of run-in period, the Week 8 visit or the visit at the time of premature termination during treatment period, and Week 1 visit or the visit at the time of premature termination during follow-up period.

(5) Bring any remaining drugs at each visit, and return them to the (sub-)investigator; and

(6) Notify the (sub-)investigator or study coordinator promptly upon facing difficulties continuing receiving the investigational drug.

7.2.2 Keeping drug-use diary

The (sub-)investigator will instruct subjects to:

(1) Enter the following information in the “drug-use diary“ every day:
- All subjects: Use status of investigational drug (run-in, treatment, and follow-up periods)
- Subfects who are allowed to use concomitant drugs: Use status of hypnotic/sedative drugs (screening, run-in, and treatment periods)

(2) Bring the "drug-use diary" to each visit, and submit it to the (sub-)investigator

7.2.3 Contraception

The (sub-)investigator will instruct subjects to prevent conception, using condom or with placement of an intrauterine device for females and in an appropriate manner such as use of condom for males. Childbearing potential female subjects and male subjects whose partner is childbearing potential will be instructed to communicate with the (sub-)investigator when the contraception is deemed uncertain. If female subject is confirmed to be pregnant from the screening period to Week 1 of the follow-up period, the (sub-)investigator will withdraw her from the screening, run-in, treatment, or follow-up period in accordance with “8.2 Withdrawal procedures for individual subjects.“ In addition, if female subject or male subject whose partner is childbearing potential is confirmed to be pregnant during treatment or follow-up period, the survey for outcome of the pregnancy will be conducted according to “12.3 Definition of serious adverse events and procedures for collecting, recording, and reporting such events” and “12.4 Follow-up survey for serious adverse events and adverse events causally related to the investigational drug.”

7.2.4 Other cautions

The (sub-)investigator will instruct subjects to:

(1) Notify the (sub-)investigator before receiving treatment given by other doctor;

(2) Avoid consuming alcohol; and

(3) Avoid using over-the-counter drugs and supplements with actions to improve sleep.

(4) Be careful when engaging in operations of machinery involving risks such as driving a car, etc.

8. Withdrawal criteria and procedures for individual subjects

8.1 Withdrawal criteria for individual subjects

When any of the following withdrawal criteria is met, the (sub-)investigator will take actions in accordance with "8.2 Withdrawal procedures for individual subjects."

8.1.1 Withdrawal criteria in the screening and run-in periods

(1) Inclusion and exclusion criteria: If the (sub-)investigator finds that any of the inclusion criteria is not met or any of the exclusion criteria is met (See "4. Inclusion and exclusion criteria of subjects")

(2) Adverse events: If the (sub-)investigator considers it difficult to continue the clinical study owing to the adverse event or if the subject wishes to discontinue the clinical study because of the adverse event

(3) Convenience of the subject: If it is difficult to continue the clinical study for convenience of the subject

(4) Others: For others, if the (sub-)investigator considers that the subject should be withdrawn from the clinical study

8.1.2 Withdrawal criteria in the treatment period

(1) Inclusion and exclusion criteria: If the (sub-)investigator finds after-the-fact that any of the inclusion criteria had not been met or any of the exclusion criteria has been met (See "4. Inclusion and exclusion criteria of subjects").

(2) Adverse events: If the (sub-)investigator considers it difficult to continue the clinical study owing to the adverse event or if the subject wishes to discontinue the study treatment because of the adverse event

(3) Convenience of the subject: If it is difficult to continue the clinical study for convenience of the subject

(4) Concomitant drugs: If a drug falling under "7.1.1 Prohibited concomitant drugs" has been indicated or administered, or a therapy falling under "7.1.2 Prohibited concomitant therapies" has been indicated, and the (sub-)investigator considers it difficult to discontinue the concerned therapy.

(5) Allowed concomitant drugs: If an allowed concomitant drug has been used in a manner falling out of provisions in "7.1.3 Allowed concomitant drugs," and the (sub-)investigator considers it difficult to ensure compliance of the concerned treatment with the provisions

(6) Inadequate response: The effect of the investigational drug is not sufficient and the (sub-)investigator determines that the study should be terminated.

(7) Number of days on dose: If the subject has taken the investigational drug on 3 days or fewer during the first week of treatment period

(8) Suicidal behavior: If a certain form of followings “suicidal behavior” (suicide attempt, and interrupted suicide attempt) has occurred as assessed according to C-SSRS

(9) Pregnancy: If the subject becomes pregnant

(10) Others: For others, if the (sub-)investigator considers that the subject should be withdrawn from the clinical study

8.1.3 Withdrawal criteria in the follow-up period

(1) Adverse events:If the (sub-)investigator considers it difficult to continue the clinical study owing to the adverse event or if the subject wishes withdrawal from the clinical study because of the adverse event

(2) Convenience of the subject: If it is difficult to continue the clinical study for convenience of the subject

(3) Pregnancy: If the subject becomes pregnant by Week 1 visit during follow-up period.

(4) Others: For others, if the (sub-)investigator considers that the subject should be withdrawn from the clinical study

8.2 Withdrawal procedures for individual subjects

If a case meeting any item of “8.1 Withdrawal criteria for individual subjects“ occurs after the initial registration, the (sub-)investigator will promptly communicate with the sponsor and proceed with the following procedures.

8.2.1 Withdrawal in screening period

(1) The clinical study for the subject will be terminated without transition to follow-up period.

(2) The (sub-)investigator will enter presence or absence of withdrawal, date of withdrawal (date on which withdrawal is determined), and reason for the withdrawal in the case report form.

8.2.2 Withdrawal in run-in period

(1) In accordance with “Table 5.2-1 Observation and test, and evaluation schedule,“ observation and evaluation scheduled at the visit at the time of premature termination in run-in period will be conducted, and the clinical study for the subject will be terminated without transition to follow-up period.

(2) The (sub-)investigator will enter presence or absence of withdrawal, date of withdrawal (date on which withdrawal is determined), and reason for the withdrawal in the case report form.

8. Withdrawal criteria and procedures for individual subjects

8.2.3 Withdrawal in treatment period

(1) In accordance with “Table 5.2-1 Observation and test, and evaluation schedule,“ observation and evaluation scheduled at the visit at the time of premature termination in treatment period will be conducted, and the subject will enter follow-up period.

(2) The (sub-)investigator will enter presence or absence of withdrawal, date of withdrawal (date on which withdrawal is determined), and reason for the withdrawal in the case report form.

8.2.4 Withdrawal in follow-up period

8.2.4.1 Before Week 1 visit during follow-up period

(1) In accordance with “Table 5.2-1 Observation and test, and evaluation schedule,“ observation and evaluation scheduled at the visit at the time of premature termination before Week 1 visit during follow-up period will be conducted, and the clinical study for the subject will be terminated.

(2) The (sub-)investigator will enter presence or absence of withdrawal, date of withdrawal (date on which withdrawal is determined), and reason for the withdrawal in the case report form.

8.2.4.2 After Week 1 visit during follow-up period

(1) In accordance with “Table 5.2-1 Observation and test, and evaluation schedule,“ observation and evaluation scheduled at the visit at the time of premature termination after Week 1 visit during follow-up period will be conducted, and the clinical study for the subject will be terminated.

(2) The (sub-)investigator will enter presence or absence of withdrawal, date of withdrawal (date on which withdrawal is determined), and reason for the withdrawal in the case report form.

8.2.5 Other points to note

If the visit is not available for the subject’s convenience, and observation, tests, and evaluation in the above section 8.2.2, 8.2.3, or 8.2.4 are not possible, the (sub-)investigator will check existence of the subject by telephone, etc. wherever possible, and enter the check result (contact is successful or not) and date of the check. In addition, the (sub-)investigator will instruct the subject to return the remainder of the investigational drug and “drug-use diary“ to the study center if he or she has these on hand.

9. Efficacy evaluation

9.1 Efficacy endpoints

The efficacy endpoints are as follows:

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

9.2 Timing and method of efficacy evaluation

Each efficacy endpoints of evaluation by the (sub-)investigator will be evaluated in accordance with "Table 5.2-1 Observation and test, and evaluation schedule. Diagnosis and evaluation in a subject will be performed by the same persons throughout the clinical study period wherever possible.

The eCOA system will be used for each efficacy evaluation by the (sub-)investigator and subjects. After study completion, the Clinical data analytics committee will store the evaluation result of each efficacy endpoints collected using eCOA system (including audit trail) in an electronic recording media (CD-ROM etc.), and provide it to the study center.

The detailed evaluation method and the method to provide electronic data to the sponsor are separately specified in the procedures.

9.2.1 MADRS

The (sub-)investigator will evaluate each subject's symptoms based on 10 MADRS items in accordance with "MADRS structured interview guide (SIGMA)."

9.2.2 HAMD17

The (sub-)investigator will evaluate each subject's symptoms based on 17 HAMD17 items in accordance with "HAM-D structured interview guide (SIGH-D)".

9.2.3 CGI-S

The (sub-)investigator will evaluate each subject's general severity of depression using CGI-S.

9.2.4 CGI-I

The (sub-)investigator will evaluate each subject's general improvement of depression compared with baseline symptoms using CGI-I.

9.2.5 $QIDS_{16}$-SR-J

Each subject will self-evaluate his/her own symptoms of depression on 16 $QIDS_{16}$-SR-J items.

9.2.6 SDS

Each subject will self-evaluate his/her social disability on 5 SDS items.

10. Safety evaluation

10.1 Safety endpoints

The safety endpoints are as follows:

(1) Adverse events

(2) General laboratory test

Hematology test: White blood cell count (WBC), red blood cell count (RBC), hemoglobin, hematocrit, and platelet count

Chemistry test: AST(GOT), ALT(GPT), ALP, gamma-GTP, LDH, total bilirubin, total protein, albumin, urea nitrogen, creatinine, total cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol, blood glucose, HbA1c, sodium, potassium, and chloride

Urinalysis (qualitative): Urine protein, urine glucose, and occult blood in urine

(3) vital signs:Sitting blood pressures (systolic/diastolic), and pulse rates

(4) Body weight

(5) Standard 12-lead ECG

(6) C-SSRS

10.2 Timing and method of safety evaluation

The (sub-)investigator will perform observation, tests, and evaluation on adverse events, general laboratory test items, vital signs, body weight, standard 12-lead ECG, and C-SSRS in accordance with “5.2 Observation and test, and evaluation schedule.“

10.2.1 Adverse events

See “12. Adverse events.“

10.2.2 General laboratory test

The (sub-)investigator will collect subjects’ blood and urine samples (See "Annex 5 Sample collection procedures" for the volume of blood and urine samples to be collected at each visit) in accordance with “Table 5.2-1 Observation and test, and evaluation schedule.” Specimens will be processed, and submitted to the central laboratory for general laboratory tests in accordance with "Annex 5 Sample collection procedures." The central laboratory will report the test results to the sponsor and study center.

The (sub-)investigator will check the test results and retain these with the original medical record (medical chart, etc.) at the study center.

10.2.3 Vital signs

The (sub-)investigator will measure sitting blood pressures (systolic/diastolic) and pulse rates in accordance with “Table 5.2-1 Observation and test, and evaluation schedule“ and enter the date of measurement and measured values in the case report form.

10.2.4 Body weight

The (sub-)investigator will measure body weight in accordance with “Table 5.2-1 Observation and test, and evaluation schedule“ and enter the date of measurement and measured value in the case report form.

10.2.5 Standard 12-lead ECG

The (sub-)investigator will measure standard 12-lead ECG on the subject at rest in the supine position in accordance with “Table 5.2-1 Observation and test, and evaluation schedule,“ and enter the date of measurement, the presence or absence of abnormal findings, and the contents of the abnormal findings if present, in the case report form.

10.2.6 C-SSRS

The (sub-)investigator will assess suicidality of the subject using C-SSRS and the eCOA system in accordance with “Table 5.2-1 Observation and test, and evaluation schedule. After study completion, the Clinical data analytics committee will store the evaluation result of each C-SSRS collected using eCOA system (including audit trail) in an electronic recording media (CD-ROM etc.), and provide it to the study center. The principal investigator will retain the results as source documents.

The detailed evaluation method and the method to provide electronic data to the sponsor are separately specified in the procedures.

11. Rater training and Clinical data analytics

11.1 Rater training

The sponsor will assign a training vendor to provide reviewer training to (sub-)investigators to equalize methods for evaluation in (1) to (6) and instruction to subjects in (7) and (8) as shown below. Only the (sub-)investigators certified by the training vendor will be qualified to make assessments in (1) to (6), and subjects instruction in (7) and (8). The (sub-)investigators certified by the training vendor shall retain the training record at the study center. Detailed equalization are separately specified in the written procedures.

(1) Diagnosis using M.I.N.I.
(2) MADRS
(3) HAMD17
(4) CGI-S
(5) CGI-I
(6) C-SSRS
(7) $QIDS_{16}$-SR-J
(8) SDS

11.2 Clinical data analytics

11.2.1 Efficacy endpoints (From the start of screening period to Week 8 visit during treatment period)

The Clinical data analytics committee will use eCOA system to obtain the efficacy assessments (See "9.2 Timing and method of efficacy evaluation"). The Clinical data analytics committee will perform the blinded review on the assessments, and report to the (sub-)investigator any dispute regarding the assessments. Also, the Clinical data analytics committee will as necessary discuss the review method with the (sub-)investigator, but in no event provide an instruction to correct the assessments; provided that the (sub-)investigator is allowed to reconsider assessments at his/her discretion based on the Clinical data analytics committee's review results. The details of the review method will be set out separately in the operating procedures.

11.2.2 Subjects' diagnosis (at the initial registration)

The (sub-)investigator will use the cCOA system to evaluate subjects' diagnosis confirmation at the initial registration. The Clinical data analytics committee will use eCOA system to obtain this assessments results. The Clinical data analytics committee will perform the blinded review on the subjects' diagnosis confirmation and report to the (sub-)investigator's. The details of the review method will be set out separately in the operating procedures.

12. Adverse events

12.1 Definition of adverse events

An adverse event is any undesirable or unintended sign (including abnormal findings in general laboratory tests,vital signs, body weight, and standard 12-lead ECG), symptom, or disorder in a subject given the investigational drug, irrespective of the causal relationship to the investigational drug. An adverse event which is judged to be causally related to the investigational drug is defined as an adverse drug reaction (ADR). In addition, any abnormal general laboratory test value meeting the following criteria is classified as an adverse event.

(1) A change in laboratory test value meets definition of serious adverse events
(2) A change in laboratory test value requires suspension or discontinuation of the investigational drug
(3) A change in laboratory test value requires medication or action for the treatment
(4) A change in laboratory test value leads to surgical intervention.
(5) Although the change in laboratory test value does not fall under the above cases, the (sub-)investigator considers the change as a medically noteworthy finding.

12.2 Survey period and items for adverse events

The (sub-)investigator will survey the following items in subjects given the investigational drug for adverse events that have occurred from the first dose of the investigational drug in treatment period to the end of follow-up period and enter the contents in the case report form.

If an adverse event has recurred after resolution of the same event but different judgements for the causal relationship to the investigational drug are given to these events, or if an adverse event that occurred before the first dose of the investigational drug has been exacerbated after that, events of the same medical term that have occurred at different timings will be entered in the case report form as separate adverse events.

(1) Name of adverse event (enter the diagnostic term where possible)
(2) Date of onset
(3) Date of resolution or date of confirmation of outcome
(4) Outcome (recovered/resolved, recovering/resolving, not recovered/not resolved, recovered/resolved with sequelae, died)
(5) Severity (mild, moderate, severe)
(6) Serious adverse event (yes or no)
(7) Action on the investigational drug (unchanged, discontinued [no re-treatment], interrupted [temporal suspension], not applicable [after the last dose of the investigational drug])
(8) Causal relationship to the investigational drug (related or unrelated)

If a serious adverse event occurs, the (sub-)investigator will prepare a “Report on serious adverse events” in accordance with “12.3 Definition of serious adverse events and procedures for collecting, recording, and reporting such events” and enter the content in the case report form. Severity and seriousness of adverse

events will be determined in accordance with “Severity/seriousness classification criteria of adverse drug reactions (PAB/PCSD Notification No. 80 dated June 29, 1992) or Common Terminology Criteria for Adverse Events v5.0 JCOG Japanese version.”

12.3 Definition of serious adverse events and procedures for collecting, recording, and reporting such events

An adverse event falling under any of (1) to (6) below irrespective of the causal relationship to the investigational drug is defined as a serious adverse event. Actions on serious adverse events are described below (See “Figure 12.3-1 Outline of procedures for reporting serious adverse events“).

(1) Event leading to death
(2) Life-threatening event
(3) Event requiring hospitalization or prolongation of hospitalization for treatment
(4) Event resulting in disability
(5) Congenital disorder or anomaly in the subsequent generations
(6) Serious event equivalent to (1) to (5)

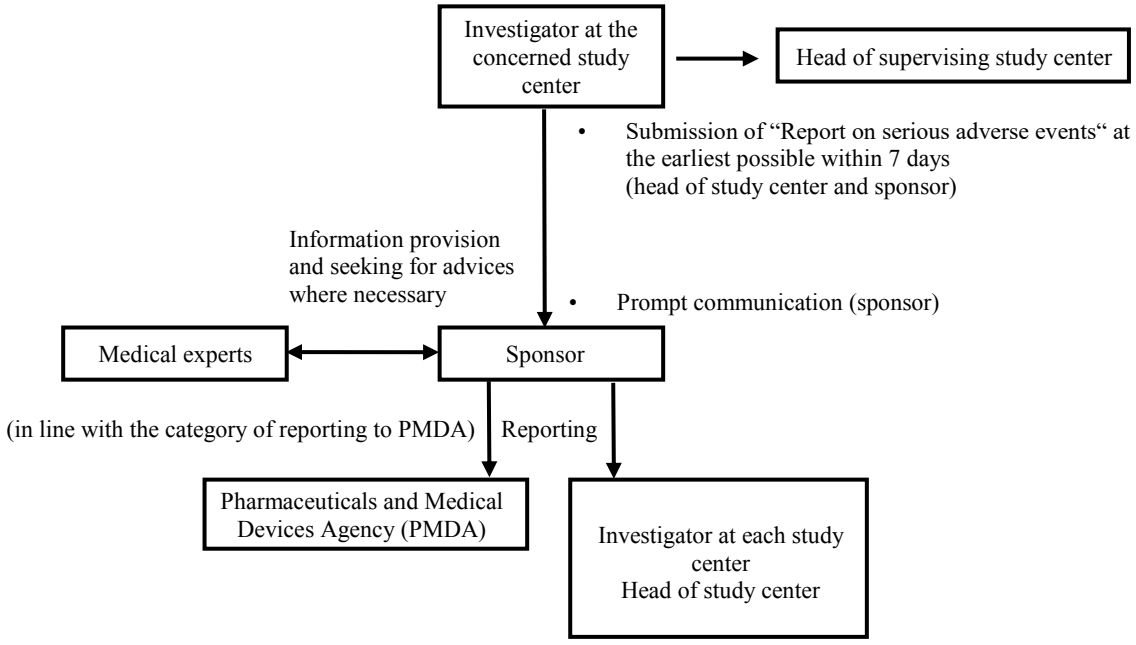


Figure 12.3-1 Outline of procedures for reporting serious adverse events

If a serious adverse event occurs, the investigator will take necessary actions on the concerned subject such as discontinuation of the investigational drug and treatment of the adverse event and proceed with the following procedures (See “Figure 12.3-1 Outline of procedures for reporting serious adverse events“).

(1) Promptly communicate the onset of the serious adverse event to the sponsor.
(2) Prepare a “Report on serious adverse events“ and submit it to the sponsor and the head of study center at the earliest possible within 7 days after communication with the sponsor.
(3) Retain a duplicate copy of the submitted report with the original medical record.

(4) Even after that, try to collect further detailed data, and report new information, if any, to the sponsor and study center.

12.4 Follow-up survey for serious adverse events and adverse events causally related to the investigational drug

(1) A follow-up survey will be conduced for the serious adverse event irrespective of the causal relationship to the investigational drug or the adverse event causally related to the investigational drug that does not resolve by the end of follow-up period, if any.

(2) The follow-up survey shall be continued until the target event resolves in principle. For any adverse event that does not resolve at 12 weeks after the end of follow-up period, the follow-up survey may be terminated, except for serious adverse events causally related to the investigational drug and adverse events causally related to the investigational drug for which the follow-up is considered necessary by the sponsor and (sub-)investigator. For these exceptional events, the follow-up survey should be continued wherever possible.

(3) The follow-up survey results obtained after the end of follow-up period may be recorded in a separate document, “Follow-up survey record on adverse events,“ without being entered in the case report form and reported to the sponsor.

13. Other survey and evaluation items

13.1 Subject baseline characteristics

The (sub-)investigator will investigate the following items at the start of screening period and enter the obtained information in the case report form.

(1) Sex
(2) Race
(3) Date of birth
(4) Date of informed consent
(5) Height
(6) Time of onset of depression
(7) Number of depressive episodes
(8) Time of onset of the current depressive episode
(9) Applicability of each of the 9 depression symptoms to DSM-5 criteria
(10) Prior treatment with antidepressant drugs for current and past depressive episodes
    1) Presence/absence of a history of treatment
    2) Name of drugs
(11) A history of treatment with hypnotics/sedatives (within 2 months before the initial registration)
    1) Presence/absence of a history of treatment
    2) Name of drugs
(12) Presence/absence of a history of treatment with antianxiety drug (within 2 months before the initial registration)

13.2 Concomitant treatment

The (sub-)investigator will survey use status of concomitant drugs and therapies throughout the clinical study period (from the start of the screening period to the end of the follow-up period). For concomitant drugs, the name, administration route, treatment duration (date of the first dose and date of the last dose), and purpose for the use will be entered in the case report form. In addition, for non-drug treatment, if applicable, the details, treatment duration (date of start of the treatment and date of end of the treatment), and the purpose will be entered in the case report form.

13.3 Comorbidities

The (sub-)investigator will survey the subject for comorbidities at each visit from the screening period to the run-in period and enter presence or absence of comorbidities and the details (if present) in the case report form.

13. Other survey and evaluation items

13.4 Pharmacokinetic evaluation

The endpoint of pharmacokinetics is the plasma desvenlafaxine concentration. The (sub-)investigator will collect blood from subjects in accordance with “Table 5.2-1 Observation and test, and evaluation schedule“ and enter, in the case report forms, the time and date of each blood collection and of the 3 nearest doses of the investigational drug pre-blood draw, as well as the presence/absence of meal within 2 hours before and after dose. Specimens will be submitted to the central laboratory for general laboratory tests, and then, from the central laboratory for general laboratory tests to the laboratory for drug concentration measurement. The laboratory for drug concentration measurement will measure the plasma desvenlafaxine concentration in the MD-120 group (50 mg and 100 mg groups) according to the separate operating procedures, and report the measurement results to the sponsor and study center after unblinding upon study completion.

13.5 Pregnancy test

The (sub-)investigator will collect urine from any premenopausal female subject at the study center in accordance with “Table 5.2-1 Observation and test, and evaluation schedule“ and perform pregnancy test to check if she is pregnant or not.

13.6 Use status of the investigational drug

The (sub-)investigator will check the drug-use status through the “drug-use diary” and interview at each visit during run-in, treatment, and follow-up periods (before Week 1 visit) and at the time of premature termination and enter the date of the first dose of the investigational drug and date of the last dose (or treatment discontinuation), and number of tablets used between the previous visit and current visit in the case report form.

14. Preparation, correction, and retention of case report forms, etc.

14.1 Target necessary for preparation of case report form

The (sub-)investigator and clinical research coordinator will prepare case report forms for subjects deemed “eligible” at the initial registration.

14.2 Structure of case report form

The case report form in this clinical study will be prepared in an electronic data capture (EDC) system.

14.3 Preparation of case report form

(1) Issuance of account for preparation of case report form

The sponsor (or person designated by the sponsor) will provide training to the (sub-)investigators and clinical research coordinators for use and entry methods of the EDC system and issue an account to such trained professional.

(2) Preparation by (sub-)investigators and clinical research coordinators

The (sub-)investigator and clinical research coordinator will prepare a case report form within an authorized range in the EDC system in accordance with the manual provided by the sponsor.

(3) Correction by (sub-)investigators and clinical research coordinators

The (sub-)investigator or clinical research coordinator will correct the content in a case report form in the EDC system if he or she consider it necessary and enter the reason. In addition, the corrected content, correcting person, and date of correct will be automatically recorded as electronic information.

(4) Electronic signature by investigator

The investigator will inspect the content in the case report form, confirm absence of any problem, and put the electronic signature in the EDC system.

14.4 Retention of case report forms

The investigator will retain electromagnetic media (CD-ROM, etc.) on the content of case report forms (including audit trails) provided by the sponsor.

14.5 Direct access to source documents

The study center and investigator will allow direct access to all the clinical study records such as source documents at monitoring and audit sessions of the sponsor as well as inspections of regulatory authorities in and outside Japan in a manner previously determined under agreement with the sponsor. In addition, the sponsor shall have a duty of confidentiality on the obtained information.

The source documents in this clinical study will be as follows:

14. Preparation, correction, and retention of case report forms, etc.

(1) Original medical record (including written informed consent, test reports, and ECG charts, etc.)
(2) All the documents related to the subject registration (including the screening list)
(3) All the documents related to diagnosis and evaluation (M.I.N.I. diagnosis results*, MADRS evaluation results*, HAMD17 evaluation results*, CGI-S and CGI-I evaluation results*, $QIDS_{16}$-SR-J evaluation results*, SDS evaluation results*, C-SSRS questionnaire results*, and diagnosis confirmation results*)
*M.I.N.I diagnostic results, MADRS, HAMD17, CGI-S, CGI-I, $QIDS_{16}$-SR-J, SDS,C-SSRS, and diagnosis confirmation results, which are directly entered in the eCOA device shall be deemed as source materials.
(4) Drug-use diary
(5) Documents related to storage of the investigational drug (including investigational drug storage table, investigational drug delivery note, and investigational drug retrieval note)

14.6 Identification of data that are directly entered in the case report form and should be classified into source documents

Not applicable in this clinical study

15. Statistical analysis

15.1 Purpose of the analysis and summary

The purpose of the analysis is to evaluate the efficacy of 8-week treatment with MD-120 in Japanese patients with depression and investigate the safety.

The efficacy will be analyzed by comparing changes in total MADRS score from the baseline to Week 8 visit during treatment period, the primary endpoint, in the MD-120 50 mg and 100 mg groups to that in the placebo group.

The safety will be analyzed based on the incidence of adverse events during treatment and follow-up periods, the primary endpoint, in each dose group.

15.2 Analysis sets

The following analysis sets will be used. The efficacy analysis set will be mainly performed on the full analysis set (FAS). The safety analysis set will be mainly performed on the safety analysis set during treatment period.

15.2.1 Efficacy analysis set

15.2.1.1 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

15.2.1.2 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 “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) Subjects who have used hypnotic/sedative drugs in compliance with provisions in “7.1.3 Allowed concomitant drugs“ from the start of sreening 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

15.2.2 Safety analysis set

15.2.2.1 Safety analysis set in 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 run-in period are available

15.2.2.2 Safety analysis set in treatment period

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 treatment period are available

15.2.2.3 Safety analysis set in 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 treatment period"

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

15.2.3 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 treatment period are available

15.3 Statistical analysis methodology

15.3.1 Features of demographic variables and other reference values

Features of demographic variables and other reference values are summarized as follows:

(1) Demographic variables

Sex, race, age (informed consent), height, body weight (at the start of screening period), and BMI

(2) Other factors

1) Age at the onset of depression
2) Period from onset of depression
3) Number of depressive episodes
4) Duration of current depressive episode
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
9) Total MADRS score, total HAMD17 score, CGI-S, and total $QIDS_{16}$-SR-J score at the baseline

15.3.2 Efficacy analysis

15.3.2.1 Analysis on primary endpoint

(1) Primary endpoint

Change in total MADRS score from baseline Week 8 visit during treatment period)

(2) Main 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 evaluation 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

(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.

15.3.2.2 Analysis on secondary endpoints

The analysis will be performed on the following endpoints.

15. Statistical analysis

(1) Response evaluated by total MADRS score at Week 8 visit during treatment period
(2) Remission evaluated by total MADRS score at Week 8 visit during treatment period
(3) Change in total HAMD17 score from baseline to Week 8 visit during treatment period
(4) Response evaluated by total HAMD17 score at Week 8 visit during treatment period
(5) Remission evaluated by total HAMD17 score at Week 8 visit during treatment period
(6) CGI-I at Week 8 visit during treatment period
(7) Response evaluated by CGI-I at Week 8 visit during treatment period
(8) Change in CGI-S from baseline to Week 8 visit during treatment period
(9) Change in total $QIDS_{16}$-SR-J score from baseline to Week 8 visit during treatment period
(10) Change in total SDS score from baseline to Week 8 visit during treatment period

15.3.3 Safety analysis

Data on adverse events will be tabulated using preferred terms (PTs) of MedDRA/J.

15.3.3.1 Analysis on primary endpoint

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

15.3.3.2 Analysis on secondary endpoints

The incidence on the following endpoint in each dose group will be calculated.

(1) Adverse drug reactions (ADRs) during treatment period and follow-up period
(2) Adverse events and ADRs during treatment period
(3) Adverse events and ADRs during follow-up period

15.3.3.3 Analysis on other endpoints

The analysis will be performed on the following endpoints.

(1) General laboratory test
(2) Vital signs
(3) Body weight
(4) Standard 12-lead ECG
(5) C-SSRS

15.3.4 Pharmacokinetic analysis

Plasma desvenlafaxine concentration at each evaluation timepoint during treatment period will be summarized for each dose group.

15.4 Target sample size and its rationale

A total of 594 subjects (n = 198 per group) will be included in the FAS.

15.5 Significance level and confidence interval

Tests on endpoints will be performed with a two-sided significance level of 5%. Interval estimation will be performed with a confidence coefficient of 0.95, and thus a two-sided 95% confidence interval will be used.

15.6 Data adoption period and conditions

Data adoption period and conditions are specified in separately prepared “Handling plan.”

15.7 Handling of missing data and abnormal specimens

15.7.1 Handling of missing data

Data missing for the analysis of the primary efficacy endpoint will be handled in accordance with the procedures specified in "15.3.2.1 Analysis on primary endpoint."

Data missing for the analysis of the secondary efficacy endpoint will be handled in accordance with the procedures specified in the "analysis plan" to be separately preprared.

For missing evaluation data other than the safety and pharmacokinetics, data at the other observation or measurement timepoint will not be substituted.

15.7.2 Handling of abnormal specimens

Abnormal specimens in 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.”

15.8 Analysis plan

Technical details related to the statistical analysis and other analyses performed where necessary are specified in separately prepared “Analysis plan.”

15.9 Procedure for reporting a change or deviation from the initial statistical analysis plan

All the changes and deviations from the initial statistical plan described in “15. Statistical analysis“ will be described in the final study report.

16. Compliance with and deviations from the study protocol as well as revision

16.1 Compliance with and deviations from the study protocol

This clinical study will be conducted in compliance with the study protocol under agreement between the investigator and sponsor. The sponsor and investigator will consult about the study protocol and put their signature or name and their seal on duplicate copies (2 copies) of the study protocol or equivalent document, and the investigator will enter the date. Furthermore, such protocol shall be approved by the institutional review board.

The (sub-)investigator is not allowed to make a deviation or change from the study protocol without the prior written agreement with the sponsor and prior approval of the institutional review board. This, however, will not apply to medically unavoidable cases (emergency deviation) such as a deviation for avoidance of an emergent risk in a subject. In a case of emergency deviation, the investigator will submit the emergency deviation report to the sponsor and the head of study center for agreement of the sponsor and approval of the institutional review board. The (sub-)investigator will record the content and reason for a deviation from the study protocol, if any.

16.2 Revision of study protocol

When any of the following cases is applicable, the sponsor shall revise the study protocol as necessary.

(1) When any of matters related to the quality, efficacy, and safety of the investigational drug and other information relevant to proper conduct of the clinical study becomes available
(2) When the study protocol has to be changed owing to medically unavoidable situation
(3) When the head of a study center directs correction based on comments from the institutional review board

The sponsor and investigator will consult about the revised study protocol and put their signature or name and their seal on duplicate copies (2 copies) of the study protocol or equivalent document, and the investigator will enter the date. Furthermore, such protocol shall be approved by the institutional review board.

After preparation of this study protocol, the following changes on Annex 1, Annex 3, and Annex 4 will be reported to the head of the study center and investigator by attaching the concerned annex as necessary, and changes on Annex 2 will be reported to the head of the study center and investigator by attaching a part of the concerned annex only including the information specific to the study center.

(1) “Administrative structure chart of the sponsor“(Annex 1)
(2) “List of study centers and investigators“ (Annex 2)
(3) “List of contract research organizations“(Annex 3)
(4) “List of prohibited concomitant drugs“(Annex 4)

17. Ethical matters

17.1 Compensation for study-related injuries

If any study-related injury occurs in a subject, the sponsor will appropriately compensate for the injury.

17.2 Protection of subjects' privacy

Adequate considerations will be given to protection of subjects' privacy, and subject identification code will be used instead of the name if a subject is identified in the case report form, etc. The prepared case report forms will be used only for this clinical study.

17.3 Handling of measurement specimens

Measurement specimens will be used only for purposes specified in this study protocol. Measurement specimens will be appropriately destroyed in accordance with the operation procedure at the laboratory or study center after end of measurement or end of storage period.

18. Criteria for prematurely terminating a part and the whole of the clinical study and the procedures

(1) If the sponsor becomes aware of information that this investigational drug may harm subjects, the company shall consider prematurely terminating a part or the whole of the clinical study in consultation with medical experts.

(2) If the sponsor decides to prematurely terminate a part or the whole of the clinical study, the company shall promptly report the above premature termination and the reason to the heads of all the study centers involved in the clinical study and PMDA in writing.

(3) Upon receipt of the report of the premature termination from the sponsor, the head of the study center will promptly notify the investigator and institutional review board of that matter in writing and give detailed explanation to them.

(4) If the clinical study is prematurely terminated, the (sub-)investigator will promptly notify the subjects of that matter, provide appropriate medical practices, and take other necessary actions.

19. Quality, retention, and publication of information

19.1 Quality control and assurance of clinical study

The quality control and assurance of the clinical study at the study center will be implemented in accordance with written procedures related to conduct of the clinical study specified by the head of the study center. In addition, any study center will accept monitoring and audit of the sponsor.

19.2 Data handling and record retention

19.2.1 Documents and records to be retained

"Documents or records related to clinical study" that should be retained at the study center will be as specified in the Good Clinical Practice (GCP) and internal provisions at the study center.

19.2.2 Retention period

The head of the study center will retain "Documents or records related to clinical study" that should be retained until the date of 1) or 2) below, whichever comes later.

(1) Date when marketing of the investigational drug is approved (or date when 3 years have elapsed since the discontinuation of development.)

(2) Date when 3 years have elapsed since premature termination or completion of the clinical study

In addition, if the sponsor requires extension of the above retention period, the head of the study center will consult with the sponsor about the retention period and method. For retention of the records, a

responsible person shall be appointed for each type of the records. In addition, when the sponsor no longer requires such retention, the company will notify the head of the study center or administrator of the institutional review board of that matter.

19.3 Laws, regulations, standards, etc. to be complied with for conduct of this clinical study

This clinical study will be conducted in compliance with the following laws, regulations, standards, etc.

(1) "Ethical principles based on Declaration of Helsinki"

(2) "Paragraph 3 of Article 14 and Article 80-2 of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics" (Law No. 145 of 1960)

(3) "Ministerial Ordinance for Enforcement of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics" (MHW Ordinance No. 1 of 1961)

(4) "Ministerial Ordinance on Good Clinical Practice for Drugs" (MHW Ordinance No.28 of March 27, 1997)

19.4 Agreement regarding publication

Publication and authors of the article will be determined through consultation between the sponsor and medical experts.

20. Payment and insurance

20.1 Payment

Actions to reduce burden of a subject associated with participation in the clinical study may be specified in writing through consultation at each study center, if such actions are taken. Matters regarding the other necessary expenses will be specified in writing through consultation separately at each study center.

20.2 Insurance

The sponsor will take actions such as insurance to ensure compensation for cost of treatment for study-related injuries and other damage incurred in the subject.

21. Study period

April 2020 to December 2022

22. Study administrative structure

22.1 Name of sponsor, address, and telephone number

Mochida Pharmaceutical Co., Ltd.

[redacted]

22.2 Person authorized to put the signature on the study protocol as a representative of the sponsor

[redacted]

22.3 Clinical study conducting manager, monitoring manager, pharmacokinetic analysis manager, data management manager, statistical analysis manager, safety information manager, and audit manager

See Annex 1

22.4 Medical expert on the sponsor

[redacted]

[Roles]

(1) Advice regarding preparation of the study protocol, investigator's brochure, and final study report
(2) Advice regarding proceeding of this clinical study, safety and efficacy evaluation, etc
(3) Assessment of causal relationship to the investigational drug and future actions for serious adverse events
(4) Advice regarding communication of revision of the study protocol, etc. or new information about this investigational drug and direction methods
(5) Advice regarding data handling
(6) Duties related to preparation of articles of this clinical study
(7) Advice regarding statistical analysis
(8) Other duties associated with (1) to (7)

22.5 Study center and investigator

See Annex 2

22.6 Registration center

[redacted]

[Roles]

(1) Preparation of written registration procedure
(2) Eligibility assessment of subject candidates for the initial registration based on the inclusion criteria and exclusion criteria for the initial registration
(3) Initial registration of subjects assessed to be eligible for the initial registration
(4) Eligibility assessment of subject candidates for second registration based on the inclusion criteria and exclusion criteria for the second registration
(5) Second registration of subjects assessed to be eligible for the second registration
(6) Eligibility assessment of subject candidates for randomization registration based on the inclusion criteria and exclusion criteria for the randomization registration
(7) Randomization registration of subjects assessed to be eligible for the randomization registration

22.7 Randomization registration center

[redacted]

[Roles]

(1) Preparation of written procedure for investigational drug randomization
(2) Preparation and storage of investigational drug assignment table for randomization and blinding of the investigational drug
(3) Preparation and storage of the investigational drug assignment table for emergency unblinding available for individual unblinding
(4) Assignment of the investigational drug (See "6.3.2 Randomization registration")
(5) Sampling of investigational drug for indistinguishability test of the investigational drug, confirmatory test after assignment of the investigational drug, assessment for conformity in approval review document
(6) Confirmation of indistinguishability at the start (after assignment of the investigational drug) and completion (after end of the follow-up period for all the subjects) of the clinical study
(7) Preparation of indistinguishability test report
(8) Duties related to unblinding (See "6.4 Procedure for unblinding with the investigational drug assignment table")

22.8 Laboratory for general laboratory tests

[redacted]

[Roles]

(1) Collection of measurement specimens for hematology test, blood biochemistry test, and urinalysis
(2) Conducting and reporting of hematology test, blood biochemistry test, and urinalysis
(3) Provision of electronic data of test results
(4) Primary storage of specimens for drug concentration measurement and their shipping arrangement to laboratory

22.9 Laboratory for drug concentration measurement

[redacted]

[Roles]

(1) Validation of measurement method of plasma desvenlafaxine concentration
(2) Measurement of plasma desvenlafaxine concentrations for this clinical study

22.10 Reviewer training, and Clinical data analyst

[redacted]

22. Study administrative structure

[redacted]

[Roles]

(1) Training and qualification of reviewers

(2) Preparation and management of eCOA

(3) Obtaining the license to use the copyright for the assessment criteria

(4) Clinical data analytics of the efficacy endpoints

(5) Clinical data analytics of subjects' diagnosis confirmation

22.11 Monitoring contract research organization

[redacted]

[Roles]

(1) Conducting of monitoring in accordance with the study protocol

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