Clinical Study Protocol

A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study of SM-13496 for the Treatment of Bipolar I Depression

Sumitomo Dainippon Pharma Co., Ltd.

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List of abbreviations and definitions of terms

The following abbreviations and special terms are used in this study protocol.

Abbreviations or special terms	Explanation
ADR	Adverse drug reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
BMI	Body mass index
BPI	Bipolarity index
BUN	Blood urea nitrogen
CGI-BP-S	Clinical Global Impression: Bipolar Version - Severity of Illness
CK	Creatine phosphokinase
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	Cytochrome P-450 enzyme
DIEPSS	Drug-Induced Extrapyramidal Symptoms Scale
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, fourth edition, Text Revision
ECG	Electrocardiography
eCRF	Electronic case report form
EDC	Electronic data capture
GCP	Good Clinical Practice
γ-GTP	γ-glutamyl transpeptidase
HAM-A	Hamilton Rating Scale for Anxiety
HbA1c	Hemoglobin A1c
HB	Hepatitis B
HCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HDL	High density lipoprotein
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
Investigator	The term "investigator" is used in this study protocol to refer to the principal investigator and/or the sub-investigator.
IRB	Institutional Review Board
IWRS	Interactive Web Response System
LDH	Lactate dehydrogenase

Abbreviations or special terms	Explanation
LDL	Low density lipoprotein
LOCF	Last observation carried forward
MADRS	Montgomery-Åsberg Depression Rating Scale
MAO	Monoamine oxidase
MedDRA	Medical Dictionary for Regulatory Activities
MINI	Mini International Neuropsychiatric Interview
ITT	Intention-to-treat
MMRM	Mixed model for repeated measurements
NGSP	National glycohemoglobin standardization program
PP	Per protocol
QOL	Quality of life
QTc	QT interval corrected
QTcB	QTc Bazett
QTcF	QTc Fridericia
RRM	Remote rater management
SAE	Serious adverse event
SDS	Sheehan Disability Scale
SSRI	Selective serotonin reuptake inhibitor
TEAE	Treatment-emergent adverse event
YMRS	Young Mania Rating Scale
WHO	World Health Organization

Protocol synopsis

Study title

A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study of SM-13496 for the Treatment of Bipolar I Depression

Objectives

(1) Primary objective

The primary objective is to compare the efficacy of SM-13496 (20-60 or 80-120 mg/day) monotherapy with that of placebo in patients with depressive symptoms associated with bipolar I disorder by assessing the change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score at Week 6.

(2) Secondary objectives

1) To evaluate the efficacy of SM-13496 (20-60 and 80-120 mg/day) monotherapy for 6 weeks in patients with depressive symptoms associated with bipolar I disorder by assessing the following
   - Change from baseline in the Clinical Global Impression: Bipolar Version - Severity of Illness (CGI-BP-S) (depression) score at Week 6
   - Change from baseline in the Sheehan Disability Scale (SDS) total score at Week 6
   - The response rate and the remission rate
2) To evaluate the time course of efficacy of SM-13496 (20-60 and 80-120 mg/day) monotherapy for 6 weeks in patients with depressive symptoms associated with bipolar I disorder by assessing the change from baseline in the MADRS total score and in the CGI-BP-S (depression) score
3) To evaluate the following
   - The efficacy for anxiety symptoms associated with bipolar I disorder by assessing the change from baseline in the Hamilton Rating Scale for Anxiety (HAM-A) total score at Week 6
   - The efficacy for manic symptoms associated with bipolar I disorder by assessing the change from baseline in the Young Mania Rating Scale (YMRS) total score at Week 6
4) To evaluate the overall safety of SM-13496 (20-60 and 80-120 mg/day) by assessing the following
   - Adverse events, adverse drug reactions
   - Laboratory measures

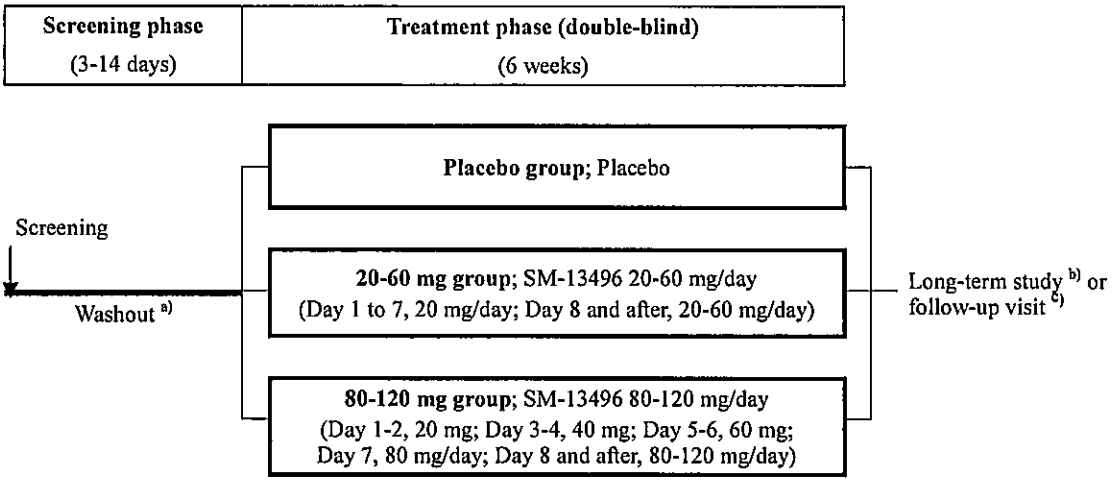
- Vital signs and electrocardiography (ECG) measurements

5) To evaluate the influence on the extrapyramidal symptoms by assessing the following
   - Extrapyramidal adverse events, extrapyramidal adverse drug reactions
   - Proportion of patients using concomitant antiparkinson drugs
   - Change from baseline in the Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS) total score (except for the overall severity score) at the final assessment
   - Change from baseline in the individual DIEPSS symptoms scores at the final assessment
6) To evaluate the influence on the following
   - QTc
   - Body weight (change from baseline in body weight at the final assessment)
   - Prolactin (change from baseline in serum prolactin concentration at the final assessment)
   - Glucose metabolism (change from baseline in fasting blood glucose, HbA1c, and glycoalbumin at the final assessment)
   - Lipid metabolism (change from baseline in total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride at the final assessment)

Study design

The study will be conducted in a multicenter, randomized, double-blind, parallel-group, placebo-controlled manner.

Study flowchart



a: If the patients receive any psychotropic drugs (eg, antipsychotics, antidepressants, mood stabilizers) at screening other than antiparkinson agents, anxiolytics, hypnotics (see Section 5.3, Page 39), all the psychotropic drugs will be terminated at least 3 days before the initiation of study treatment after titrated down as needed.
b: The patients who complete the 6-week treatment phase will proceed to the long-term study after being deemed eligible and providing written informed consent to participate in the study.
c: Patients who are not enrolled in the long-term study will visit the study site for a follow-up 7 days (± 2 days) after the final administration of study drug.

Subjects

Patients with major depressive episodes associated with bipolar I disorder

Inclusion criteria

1) Patients who were fully informed of and understand the objectives, procedures, and possible benefits and risks of the study and who provided written voluntary consent to participate in the study. If the patient is a minor at the time of consent, written consent should be obtained from a legally acceptable representative (guardian) in addition to the patient him/herself.
2) Outpatients aged 18 through 74 years at informed consent.
3) Patients with bipolar I disorder, most recent episode depressed, with or without rapid cycling disease course (≥ 4 episodes of mood disturbance but < 8 episodes in the 12 months prior to screening), and without psychotic features (diagnosed by the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, Text Revision [DSM-IV-TR] criteria and confirmed by the Mini International Neuropsychiatric Interview [MINI]).
4) Patients who have a history of at least one manic or mixed episode (preferably with confirmation by a reliable informant, such as a family member or

caregiver).

5) Patients whose current major depressive episode is ≥ 4 weeks and < 12 months in duration at screening.
6) Patients with a rater-administered MADRS total score of ≥ 20 and a computer-administered MADRS total score of ≥ 20 at both screening and baseline.
7) Patients with a YMRS total score of ≤ 12 at both screening and baseline.
8) Patients with a negative pregnancy test at screening, when the patients are female and of childbearing potential.
9) Patients who agree to use appropriate contraception (see Section 5.6, Page 44) to prevent pregnancy in female patients and the female partners of patients, when the patients or their partners are of childbearing potential.
10) Patients whose dosage of the following concomitant drugs remains unchanged for the specified duration as follows:
   - The dose of oral hypoglycemic drugs or antihypertensive drugs remained unchanged for at least 30 days prior to screening.
   - The dose of thyroid hormone (replacement therapy) remained unchanged for at least 90 days prior to screening.
   - The dose of drugs for complications (other than the above-mentioned drugs) have been stable (within ± 25%) for at least 30 days prior to screening.
   - The content of psychotherapy and cognitive behavioral therapy remained unchanged for at least 12 weeks prior to screening.

Exclusion criteria

1) Patients who were diagnosed as having an Axis I or Axis II disorder (DSM-IV-TR criteria) other than bipolar I disorder that is the primary focus of treatment within 3 months prior to screening.
2) Patients with a score of ≥ 4 on the MADRS item 10 (suicidal thoughts) at screening or baseline.
3) Patients with a "Yes" response to the Columbia-Suicide Severity Rating Scale (C-SSRS) item 4 (active suicidal ideation with some intent to act, without specific plan) or item 5 (active suicidal ideation with specific plan and intent) at screening (within 6 months prior to screening) or baseline.
4) Patients with imminent risk of suicide or injury to self, others, or property.
5) Patients for whom diagnostic agreement (based on the Bipolarity Index) between the investigator and Bracket (Pennsylvania, the United States), the agency for computerized diagnosis, cannot be reached.

6) Patients with a history of non-response to 6-week trial of 3 or more antidepressants (with or without concomitant use of mood stabilizers) during the current episode.
7) Patients who had been hospitalized because of a manic or mixed episode within 60 days prior to screening.
8) Patients who received monoamine oxidase (MAO) inhibitor within 21 days prior to screening.
9) Patients who received fluoxetine or a combination of olanzapine and fluoxetine within 28 days prior to screening.
10) Patients who received any depot antipsychotics (sustained-release formulation) within 90 days prior to screening.
11) Patients who received clozapine within 120 days prior to screening.
12) Patients who received electroconvulsive therapy within 90 days prior to screening.
13) Patients with a ≥ 25% reduction in the MADRS total score between screening and baseline.
14) Patients with a history of HIV seropositivity.
15) Patients with a history of alcohol/drug abuse (DSM-IV-TR criteria) within 3 months prior to screening or of alcohol/drug dependence (DSM-IV-TR criteria) within 12 months prior to screening. Exceptions include caffeine or nicotine abuse/dependency.
16) Patients with a history of hypersensitivity (eg, drug-induced anaphylaxis, rash, urticaria, or other allergic reactions) to more than one distinct chemical class of drug.
17) Patients with previous or existing clinically significant complications, such as serious nervous system, endocrine system (eg, type I diabetes mellitus), hepatic, renal, hematological, respiratory, cardiovascular (eg, unstable angina, congestive heart failure), gastrointestinal, urological, or other diseases. Patients who have a history of any of such diseases and who are considered ineligible for the study by the investigator.
18) Patients with acute hepatitis, severe chronic hepatitis or marked hepatic dysfunction. When the hepatitis screening test is positive, the investigator should evaluate carefully patient eligibility on the basis of his or her medical history or other laboratory data.
19) Patients with a gastrointestinal disease or a surgical history that may affect drug absorption, distribution, metabolism, or excretion.

20) Patients with any chronic organic disease of the central nervous system (ie, tumor, inflammation, convulsive seizure, vascular disorders, Parkinson's disease, Alzheimer's disease or other type of dementia, myasthenia gravis, or other degenerative diseases) .
21) Patients with any mental retardation or persistent neurological findings due to serious head injury.
22) Patients with a BMI of ≤ 18 kg/m^2 or ≥ 40 kg/m^2 at screening.
23) Patients with previous or existing macular or retinal pigment changes.
24) Patients with a previous (within 5 years prior to screening) or existing malignant tumor (excluding appropriately treated basal cell carcinoma of the skin, squamous cell carcinoma, and uterine cervix cancer).
25) Patients with a history of neuroleptic malignant syndrome.
26) Patients with severe tardive dyskinesia, severe dystonia, or other severe motor dysfunction.
27) Patients with an HbA1c (NGSP) value of 8.4% or higher at screening.
28) Patients with a history or presence of clinically significant ECG abnormality.
29) Patients who have received the study medication (including placebo) in a previous clinical study of SM-13496.
30) Patients who are breastfeeding.
31) Patients who are currently participating or participated in a clinical study with an investigational or marketed compound or device within 3 months prior to screening or who participated in 3 or more clinical studies within 12 months prior to screening.
32) Patients who are otherwise considered ineligible for the study by the investigator.

Study drug

SM-13496 20 mg tablets and placebo tablets will be used. SM-13496 20 mg tablets are white film-coated tablets containing 20 mg of lurasidone HCl. The placebo formulation will match the active drug tablets (SM-13496 20 mg) in all outward physical characteristics.

Dosage and treatment duration

The study drug administration will be initiated on the day after randomization. In the 20-60 mg group, SM-13496 will be administered at a dose of 20 mg/day for 1 week (starting on Day 1), and at a flexible dose within a range of 20 to 60 mg/day for 5 weeks (starting on Day 8). In the 80-120 mg group, SM-13496 will be administered at a dose of 20 mg/day on Days 1 and 2 and the dose will be increased by 20 mg/day

every 2 days on Days 3 to 7 (ie, 40 mg on Days 3 and 4, 60 mg on Days 5 and 6, and 80 mg on Day 7). SM-13496 will be administered at a flexible dose within a range of 80 to 120 mg/day for 5 weeks (starting on Day 8). In the placebo group, the placebo will be administered for 6 weeks. The study drug will be administered orally within 30 minutes after evening meal once daily.

The dose can be increased or decreased by 20 mg/day at the scheduled visits. At the scheduled visits at Week 1 or after, when no safety concerns are found and the CGI-BP-S (depression) score is within a range from 5 (markedly ill) to 7 (very severely ill), the dose should in principle be increased. When any safety concerns are raised, the dose can be reduced by 20 mg/day at unscheduled visits. Dose increases will be not permitted at unscheduled visits.

Concomitant medications and therapies

	Screening phase	Treatment phase	Follow-up
CYP3A4 inhibitors and inducers	A	A	C
Clozapine	A	A	C
Depot antipsychotics	A	A	C
MAO inhibitors	A	A	C
Other investigational products and post-marketing clinical study drugs	A	A	A
Chinese herbal medication	A	A	C
Ginkgo Biloba extract, Kava Kava, St. John's wort	A	A	C
Electroconvulsive therapy	A	A	C
Psychotropic medications (excluding antiparkinson drugs, anxiolytics, and hypnotics)	B	A	C
Medications for extrapyramidal symptoms	B	B	C
Anxiolytics	B	B	C
Hypnotics	B	B	C
Medications for complications	B	B	C
Psychotherapy and cognitive behavioral therapy	B	B	C

A, Prohibited; B, Restricted; C, No restrictions

Investigation, measurements, assessments, and study schedule

		Screening phase	Baseline	Treatment phase (double-blind)							Follow-up visit
Study Visit No.	-	1	2	3	4	5	6	7	8 [a]	Dis-continuation [a]	-
Study timeline (week)	-	-	Day −1	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	-	-
Visit window (Day) [b]		−14 to −3	−1	5 to 9	12 to 16	19 to 23	26 to 30	33 to 37	39 to 45	-	- [c]
Obtain written informed consent	X [d]										
Medical history		X									
Inclusion/Exclusion criteria		X	X								
IWRS		X	X	X	X	X	X	X	X [e]	X [e]	
Randomization			X								
Dispense study drug			X	X	X	X	X	X			
Treatment compliance				X	X	X	X	X	X	X	
BPI		X									
MINI		X									
MADRS		X	X	X	X	X	X	X	X	X	
CGI-BP-S		X	X	X	X	X	X	X	X	X	
SDS			X						X	X	
HAM-A			X						X	X	
YMRS		X	X	X	X	X	X	X	X	X	
C-SSRS		X	X	X	X	X	X	X	X	X	
DIEPSS			X	X	X	X	X	X	X	X	
Height		X									
Body weight		X	X						X	X	
Body temperature, blood pressure, pulse rate		X	X	X	X	X	X	X	X	X	
12-lead ECG		X	X						X	X	
Laboratory measures		X	X [f]	X			X		X [f]	X [f]	
Hepatitis screening		X									
Urine pregnancy test (female) [g]		X							X	X	
Serum pregnancy test (female) [h]		X							X	X	

		Screening phase	Baseline	Treatment phase (double-blind)							Follow-up visit
Study Visit No.	-	1	2	3	4	5	6	7	8 [a]	Dis-continuation [a]	-
Study timeline (week)	-	-	Day −1	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	-	-
Visit window (Day) [b]		−14 to −3	−1	5 to 9	12 to 16	19 to 23	26 to 30	33 to 37	39 to 45	-	- [c]
SM-13496 serum concentration measurements [i]						X	X		X	X [j]	
Physical examination/adverse event monitoring		X	X	X	X	X	X	X	X	X	X

a) At Visit 8 (Week 6) and at discontinuation, all assessments and tests should be performed within 72 hours after the final administration of the study drug.
b) Day 1 is defined as the day of the initial administration in the treatment phase and Day −1 is defined as the day before Day 1.
c) Only for patients who discontinue the present study or who will not proceed to the long-term study. Such patients will visit the study site for a follow-up 7 days (± 2 days) after Visit 8 (Week 6) or after discontinuation.
d) Informed consent can be obtained at Visit1, but must be done prior to interventional study procedures.
e) The patient's final status will be marked in the IWRS at Visit 8 or at discontinuation.
f) Blood will be collected in fasting condition (fasting for at least 10 hours before blood sampling on the day of the scheduled visit).
g) To be performed only in female patients of childbearing potential before menopause.
h) To be performed only in the case of positive urine pregnancy test.
i) To be performed only in patients who provided written informed consent. Blood samples will be collected at Visit 5 (Week 3), Visit 6 (Week 4), and Visit 8 (Week 6), and at discontinuation (if after Week 3) at 13 to 15 hours after the administration of the study drug on the day prior to each of these visit days.
j) To be performed only if the discontinuation visit occurs after Week 3

Variables

1. Efficacy variables

(1) Primary variable

- Change from baseline in the MADRS total score at Week 6

(2) Secondary variables

- Change from baseline in the MADRS total score at each assessment
- Change from baseline in the CGI-BP-S (depression) score at Week 6 and each assessment point
- Change from baseline in the SDS total score at Week 6
- Change from baseline in the YMRS total score at Week 6 and each assessment point
- Change from baseline in the HAM-A total score at Week 6
- Treatment response rate (proportion of patients who achieve a $\geq$ 50% reduction from baseline in the MADRS total score) at Week 6
- Symptom remission rate (proportion of patients who achieve a MADRS total score of $\leq$ 12) at Week 6

2. Pharmacokinetic variables

- Serum concentration of SM-13496
- Serum concentrations of major metabolites (hydroxylated products [ID-14283 and ID-14326], cleaved product [ID-11614])

3. Safety variables

- Incidence of Adverse events (AEs) and Adverse drug reactions (ADRs)
- Incidence of extrapyramidal AEs and ADRs
- Proportion of patients with concomitant use of antiparkinson medication.
- Change from baseline in the DIEPSS total score (except for the overall severity score) at the final assessment
- Change from baseline in the individual DIEPSS symptoms scores at the final assessment
- Change from baseline in the serum prolactin concentration at the final measurement
- Change from baseline in ECG parameter (QTc) at the final measurement
- Change from baseline in fasting blood glucose, HbA1c (NGSP), glycoalbumine, total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides at the final measurement
- Change from baseline in body weight at the final measurement
- Laboratory measures and vital signs

- Proportion of patients with a YMRS total score of ≥ 16 at 2 or more consecutive assessments or with any adverse events related to mania symptoms
- Proportion of patients with any instance of suicide attempt or suicidal ideation based on the C-SSRS.

Target number of patients

501 (ie, 167 patients per treatment group)

Planned duration of the study

July 2013 to April 2017 (Enrollment: September 2013 to December 2016)

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Appendix

Appendix A: Study administrative structure
Appendix B: Investigator agreement

1. Background

Bipolar disorder is a mood disorder with symptoms of excessive fluctuations in mood, emotion, and drive, and typically characterized by repeated occurrence of manic or hypomanic episodes and major depressive episodes. The core symptoms of manic or hypomanic episodes include abnormally elevated, expansive or irritable mood, and those of major depressive episodes include depressed mood and loss of interest or pleasure. According to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, Text Revision (DSM-IV-TR), bipolar disorder can be classified broadly into two types: bipolar I and II disorder. Bipolar I disorder involves manic episodes and major depressive episodes, while bipolar II disorder involves hypomanic episodes and major depressive episodes. The lifetime prevalence of bipolar I disorder varies from 0.2% to 2.0% [1] in various countries, and is reported to be 0.5% [2] in Japan.

In the DSM-IV-TR, bipolar depressive state is defined as "the current (or most recent) major depressive episode with a history of at least one manic or mixed episode." An observation study [3),4)] shows that the patients with bipolar I disorder had depressive symptoms for 32% of the followed duration (longer than 10 years) and manic/hypomanic symptoms for 9% of the duration, and that the patients with bipolar II disorder had depressive symptoms for 50% of the duration and manic/hypomanic symptoms for 1% of the duration. The study results indicate that the depressive state was predominant. Since frequent depressive episodes associated with bipolar disorder significantly interfere with social functioning and family life, the depressive state can impair the quality of life (QOL) [5),6)]. In addition, the suicide rate among patients with bipolar I disorder has been reported to be approximately 10% to 15%, and most suicides are committed in the depressive or mixed state [7)]. Given the impact on QOL and high suicide rates, treatment of depressive symptoms associated with bipolar disorder is very important.

For depressive symptoms associated with bipolar disorder, the guideline [8)] issued jointly by the Canadian Network for Mood and Anxiety Treatments and the International Society for Bipolar Disorders recommend the following drugs as first-line treatments: lithium (alone or in combination with divalproex, a selective serotonin reuptake inhibitor [SSRI], or bupropion), lamotrigine, quetiapine, olanzapine-fluoxetine combination, divalproex (in combination with an SSRI or bupropion). In Japan, the treatment guideline by the Japanese Society of Mood Disorders [9)] recommends quetiapine, lithium, olanzapine, and lamotrigine as first-line treatments; however, only olanzapine is approved for this indication. Moreover, these

currently available drugs are known to have side effects. For example, olanzapine and quetiapine are associated with adverse reactions such as increased weight and abnormal glucose metabolism. Lamotrigine may cause adverse reactions such as serious skin disorders (eg, Stevens-Johnson syndrome). Lithium may cause adverse reactions such as renal disorder and thyroid dysfunction, and furthermore it requires blood concentration monitoring to prevent intoxication.

Lurasidone HCl (SM-13496) is a novel atypical antipsychotic synthesized by Sumitomo Pharmaceuticals Co., Ltd. (currently Sumitomo Dainippon Pharma Co., Ltd.). It has a high binding affinity for dopamine D_2 and serotonin 5-HT_{2A} receptors, which relate to antipsychotic effects, and 5-HT_7 receptor, which may relate to antidepressant effect and cognitive function [10], and the 5-HT_{1A} receptor, which may relate to anxiolytic effect and cognitive function [10]. Therefore, lurasidone is expected to have not only antipsychotic effects but also antidepressant and anxiolytic effects.

In the United States and Canada, lurasidone has been approved for the treatment of schizophrenia. In Europe, an application for marketing approval was filed in 2012. In Japan, a multinational phase 3 study in patients with schizophrenia is ongoing.

In the United States, placebo-controlled, phase 3 studies in patients with depressive symptoms associated with bipolar I disorder have been completed. In the PREVAIL 2 study (D1050236), 20-60 or 80-120 mg/day of SM-13496, or placebo was administered as monotherapy for 6 weeks. The reduction in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score (the primary variable) was significantly greater for SM-13496 than for placebo. In the PREVAIL 1 study (D1050235), 20-120 mg/day of SM-13496 or placebo was administered with lithium or divalproex for 6 weeks. The reduction in the MADRS total score was significantly greater for SM-13496 than for placebo. In both studies, the efficacy of SM-13496 for depressive symptoms associated with bipolar I disorder was confirmed. No notable safety issues were found for 20-120 mg/day of SM-13496. On the basis of these data, the monotherapy and adjunctive therapy with lithium or valproate for depressive symptoms associated with bipolar disorder was approved in the United States in 2013 and is under regulatory authority's review in Canada.

On the basis of the above-mentioned background, the clinical development of SM-13496 for depressive symptoms associated with bipolar disorder has been initiated in Japan as well. A placebo-controlled phase 3 study has been planned to evaluate the

efficacy and safety of SM-13496 monotherapy at doses of 20-60 or 80-120 mg/day, at the same doses the efficacy was confirmed in the PREVAIL 1 and 2 studies. The primary variable will be the change in the MADRS total score, and the duration of treatment will be 6 weeks. Patients completing the present study can be enrolled in a long-term study (Study D1002002) to evaluate the long-term safety and efficacy of SM-13496.

2. Objectives

2.1 Primary objective

The primary objective is to compare the efficacy of SM-13496 (20-60 or 80-120 mg/day) monotherapy with that of placebo in patients with depressive symptoms associated with bipolar I disorder by assessing the change from baseline in the MADRS total score at Week 6.

2.2 Secondary objectives

The secondary objectives of the study are as follows;

1) To evaluate the efficacy of SM-13496 (20-60 and 80-120 mg/day) monotherapy for 6 weeks in patients with depressive symptoms associated with bipolar I disorder by assessing the following
   - Change from baseline in the Clinical Global Impression: Bipolar Version - Severity of Illness (CGI-BP-S) (depression) score at Week 6
   - Change from baseline in the Sheehan Disability Scale (SDS) total score at Week 6
   - The response rate and the remission rate
2) To evaluate the time course of efficacy of SM-13496 (20-60 and 80-120 mg/day) monotherapy for 6 weeks in patients with depressive symptoms associated with bipolar I disorder by assessing the change from baseline in the MADRS total score and in the CGI-BP-S (depression) score
3) To evaluate the following
   - The efficacy for anxiety symptoms associated with bipolar I disorder by assessing the change from baseline in the Hamilton Rating Scale for Anxiety (HAM-A) total score at Week 6
   - The efficacy for manic symptoms associated with bipolar I disorder by assessing the change from baseline in the Young Mania Rating Scale (YMRS) total score at Week 6

4) To evaluate the overall safety of SM-13496 (20-60 and 80-120 mg/day) by assessing the following
   - Adverse events, adverse drug reactions
   - Laboratory measures
   - Vital signs and electrocardiography (ECG) measurements
5) To evaluate the influence on the extrapyramidal symptoms by assessing the following
   - Extrapyramidal adverse events, extrapyramidal adverse drug reactions
   - Proportion of patients using concomitant antiparkinson drugs
   - Change from baseline in the Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS) total score (except for the overall severity score) at the final assessment
   - Change from baseline in the individual DIEPSS symptoms scores at the final assessment
6) To evaluate the influence on the following
   - QTc
   - Body weight (change from baseline in body weight at the final assessment)
   - Prolactin (change from baseline in serum prolactin concentration at the final assessment)
   - Glucose metabolism (change from baseline in fasting blood glucose, HbA1c, and glycoalbumin at the final assessment)
   - Lipid metabolism (change from baseline in total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride at the final assessment)

3. Study design and flowchart

3.1 Study design

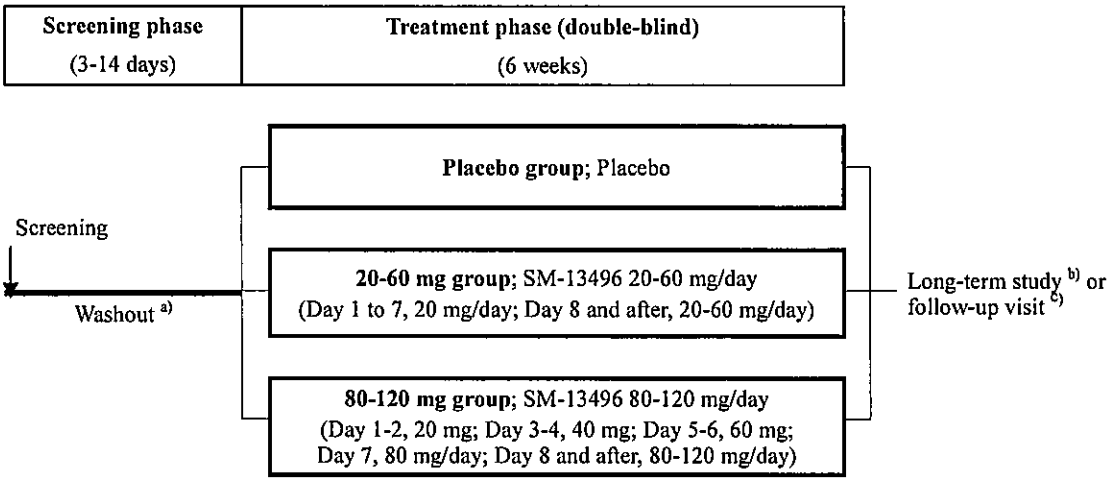
The study will be conducted in a multicenter, randomized, double-blind, parallel-group, placebo-controlled manner.

3.2 Study method and flowchart

3.2.1 Flowchart and study schedule

The study flowchart is shown in Figure 1. This study consists of the screening phase and the treatment phase. The long-term study (Study D1002002) will follow the present study.

Figure 1 Study flowchart



a: If the patients receive any psychotropic drugs (eg, antipsychotics, antidepressants, mood stabilizers) at screening other than antiparkinson agents, anxiolytics, hypnotics (see Section 5.3, Page 39), all the psychotropic drugs will be terminated at least 3 days before the initiation of study treatment after titrated down as needed.
b: The patients who complete the 6-week treatment phase will proceed to the long-term study after being deemed eligible and providing written informed consent to participate in the study.
c: Patients who are not enrolled in the long-term study will visit the study site for a follow-up 7 days (± 2 days) after the final administration of study drug.

(1) Screening phase (3 to 14 days)

In the screening period, prior psychotropic drugs will be washed-out. If the patients receive any psychotropic drugs (eg, antipsychotics, antidepressants, mood stabilizers) at screening other than permitted concomitant antiparkinson agents, anxiolytics, hypnotics (see Sections 5.3, Page 39), these drugs will be terminated at least 3 days before the initiation of study treatment after titrated down as needed.

(2) Treatment phase (6 weeks)

After randomization, patients will receive 20-60 mg/day of SM-13496 (20-60 mg group), 80-120 mg/day of SM-13496 (80-120 mg group), or placebo (placebo group) for 6 weeks in a double-blind fashion.

Rationale

The washout period was designed to eliminate the effects of prior psychotropic drugs and to enable appropriate evaluation of the efficacy and safety of the study treatment. The duration of the period is at least 3 days by considering the duration of the same period in the PREVAIL 2 study and in other studies [11] in patients with major depressive symptoms associated with bipolar I disorder.

The study schedule is shown in Table 1. Day 1 is defined as the day of the initial administration in the treatment phase and Day –1 is defined as the day before Day 1.

Table 1 Study schedule

		Screening phase	Baseline	Treatment phase (double-blind)							Follow-up visit
Study Visit No.	-	1	2	3	4	5	6	7	8 [a]	Dis-continuation [a]	-
Study timeline (week)	-	-	Day −1	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	-	-
Visit window (Day) [b]		−14 to −3	−1	5 to 9	12 to 16	19 to 23	26 to 30	33 to 37	39 to 45	-	- [c]
Obtain written informed consent	X [d]										
Medical history		X									
Inclusion/Exclusion criteria		X	X								
IWRS		X	X	X	X	X	X	X	X [e]	X [e]	
Randomization			X								
Dispense study drug			X	X	X	X	X	X			
Treatment compliance				X	X	X	X	X	X	X	
BPI		X									
MINI		X									
MADRS		X	X	X	X	X	X	X	X	X	
CGI-BP-S		X	X	X	X	X	X	X	X	X	
SDS			X						X	X	
HAM-A			X						X	X	
YMRS		X	X	X	X	X	X	X	X	X	
C-SSRS		X	X	X	X	X	X	X	X	X	
DIEPSS			X	X	X	X	X	X	X	X	
Height		X									
Body weight		X	X						X	X	
Body temperature, blood pressure, pulse rate		X	X	X	X	X	X	X	X	X	
12-lead ECG		X	X						X	X	
Laboratory measures		X	X [f]	X			X		X [f]	X [f]	
Hepatitis screening		X									
Urine pregnancy test (female) [g]		X							X	X	
Serum pregnancy test (female) [h]		X							X	X	

		Screening phase	Baseline	Treatment phase (double-blind)							Follow-up visit
Study Visit No.	-	1	2	3	4	5	6	7	8 [a)]	Dis-continuation [a)]	-
Study timeline (week)	-	-	Day −1	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	-	-
Visit window (Day) [b)]		−14 to −3	−1	5 to 9	12 to 16	19 to 23	26 to 30	33 to 37	39 to 45	-	- [c)]
SM-13496 serum concentration measurements [i)]						X	X		X	X [j)]	
Physical examination/adverse event monitoring		X	X	X	X	X	X	X	X	X	X

a) At Visit 8 (Week 6) and at discontinuation, all assessments and tests should be performed within 72 hours after the final administration of the study drug.
b) Day 1 is defined as the day of the initial administration in the treatment phase and Day −1 is defined as the day before Day 1.
c) Only for patients who discontinue the present study or who will not proceed to the long-term study. Such patients will visit the study site for a follow-up 7 days (± 2 days) after Visit 8 (Week 6) or after discontinuation.
d) Informed consent can be obtained at Visit1, but must be done prior to interventional study procedures.
e) The patient's final status will be marked in the IWRS at Visit 8 or at discontinuation.
f) Blood will be collected in fasting condition (fasting for at least 10 hours before blood sampling on the day of the scheduled visit).
g) To be performed only in female patients of childbearing potential before menopause.
h) To be performed only in the case of positive urine pregnancy test.
i) To be performed only in patients who provided written informed consent. Blood samples will be collected at Visit 5 (Week 3), Visit 6 (Week 4), and Visit 8 (Week 6), and at discontinuation (if after Week 3) at 13 to 15 hours after the administration of the study drug on the day prior to each of these visit days.
j) To be performed only if the discontinuation visit occurs after Week 3

3.3 Dosage

The study drug administration will be initiated on the day after randomization. In the 20-60 mg group, SM-13496 will be administered at a dose of 20 mg/day for 1 week (starting on Day 1), and at a flexible dose within a range of 20 to 60 mg/day for 5 weeks (starting on Day 8). In the 80-120 mg group, SM-13496 will be administered at a dose of 20 mg/day on Days 1 and 2 and the dose will be increased by 20 mg/day every 2 days on Days 3 to 7 (ie, 40 mg on Days 3 and 4, 60 mg on Days 5 and 6, and 80 mg on Day 7). SM-13496 will be administered at a flexible dose within a range of 80 to 120 mg/day for 5 weeks (starting on Day 8). In the placebo group, the placebo will be administered for 6 weeks. The study drug will be administered orally within 30 minutes after evening meal once daily.

The dose can be increased or decreased by 20 mg/day at the scheduled visits. At the scheduled visits at Week 1 or after, when no safety concerns are found and the CGI-BP-S (depression) score is within a range from 5 (markedly ill) to 7 (very severely ill), the dose should in principle be increased. When any safety concerns are raised, the dose can be reduced by 20 mg/day at unscheduled visits. Dose increases will be not permitted at unscheduled visits.

Rationale

The same dose regimens of SM-13496 as in the PREVAIL 2 study (20-60 mg/day and 80-120 mg/day) were selected because the efficacy of the 2 regimens was superior to that of placebo. CYP3A4, the main metabolizing enzyme for SM-13496, has no genetic polymorphism that causes marked differences in metabolizing activity. The pharmacokinetic profiles in Japanese and in people outside Japan are similar. Furthermore, no notable differences in the diagnostic criteria for bipolar disorder and clinical therapies are found between Asia, Europe, and the United States. No notable differences in clinical doses for the treatment of bipolar disorder are expected between Asia, Europe, and the United States. Therefore, the same dose regimens as in the PREVAIL 2 study were selected.

Since a low initial dose followed by a gradual dose escalation is preferable from the safety point of view, 20 mg/day was selected as the initial dose for both regimens. The flexible-dose manner was selected because individual differences in patient condition and symptoms associated with bipolar I disorder vary.

The same dose timing every day is preferable for appropriate evaluation of efficacy and safety. The study drug will be administered after an evening meal because of the food effect for SM-13496.

In the PREVAIL 2 study, in which the study drug was administered for 6 weeks, the efficacy of SM-13496 was superior to that of placebo (the primary variable, the change in the MADRS total score). Furthermore, the duration of treatment should be as short as possible because the placebo group is included in the study. Therefore, 6 weeks were selected as the shortest treatment duration possible to adequately evaluate efficacy and safety.

3.4 Variables

3.4.1 Efficacy variables

3.4.1.1 Primary variable

The primary variable of the study is the change from baseline in the MADRS total score at Week 6

Rationale

The MADRS [11] is a 10-item subscale for the evaluation of depressive symptoms and has been derived from the 65 symptoms items in the Comprehensive Psychopathological Rating Scale (CPRS). The MADRS is a scale that can appropriately assess the anti-depressive efficacy of a medication by a uni-dimensional evaluation of psychological symptoms excluding physical symptoms and has been used in many clinical studies [12), 13)].

3.4.1.2 Secondary variables

- Change from baseline in the MADRS total score at each assessment
- Change from baseline in the CGI-BP-S (depression) score at Week 6 and each assessment point
- Change from baseline in the SDS total score at Week 6
- Change from baseline in the YMRS total score at Week 6 and each assessment point
- Change from baseline in the HAM-A total score at Week 6
- Treatment response rate (proportion of patients who achieve a $\geq$ 50% reduction from baseline in the MADRS total score) at Week 6
- Symptom remission rate (proportion of patients who achieve a MADRS total score of $\leq$ 12) at Week 6

Rationale

The CGI-BP-S [14] is a scale that assesses the overall severity of bipolar disorder and consists of 3 different parts; depression, mania, and overall to accurately evaluate bipolar disorder symptoms. The CGI-BP-S (depression) was selected for an overall assessment of efficacy against depressive symptoms associated with bipolar disorder. The SDS [15] consists of self-rated items designed to assess functional impairments in 3 domains of daily life (work/school, social life, and communication with the family). The SDS is easy to use and is not easily influenced by the patient's severity of illness or willingness to use the scale. The YMRS [16] is an 11-item scale designed to assess severity of manic symptoms, and frequently used in clinical studies [12), 13)]. The HAM-A [17] is a 14-item scale developed to assess psychological anxiety (frustrations or psychological stress) and somatic anxiety (physical symptoms associated with anxiety). It is reliable and frequently used in clinical trials [12), 13)]. The treatment response rate and symptom remission rate are frequently used for the assessment of efficacy of antipsychotics.

3.4.2 Pharmacokinetic variables

- Serum concentration of SM-13496
- Serum concentrations of major metabolites (hydroxylated products [ID-14283 and ID-14326], cleaved product [ID-11614])

Rationale

Serum concentrations of SM-13496 and corresponding metabolites will be measured to compare the pharmacokinetic profiles among the participating countries.

3.4.3 Safety variables

- Incidence of Adverse events (AEs) and Adverse drug reactions (ADRs)
- Incidence of extrapyramidal AEs and ADRs
- Proportion of patients with concomitant use of antiparkinson medication.
- Change from baseline in the DIEPSS total score (except for the overall severity score) at the final assessment
- Change from baseline in the individual DIEPSS symptoms scores at the final assessment
- Change from baseline in the serum prolactin concentration at the final measurement
- Change from baseline in ECG parameter (QTc) at the final measurement

- Change from baseline in fasting blood glucose, HbA1c (NGSP), glycoalbumine, total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides at the final measurement
- Change from baseline in body weight at the final measurement
- Laboratory measures and vital signs
- Proportion of patients with a YMRS total score of $\geq$ 16 at 2 or more consecutive assessments or with any adverse events related to mania symptoms
- Proportion of patients with any instance of suicide attempt or suicidal ideation based on the Columbia-Suicide Severity Rating Scale (C-SSRS).

Rationale

Extrapyramidal symptoms are the most common side effects associated with antipsychotics and usually treated with antiparkinson drugs. The DIEPSS [18] is an evaluation scale for the extrapyramidal symptoms. Antipsychotics are known to increase serum prolactin concentration [19]. Some atypical antipsychotics are known to influence glucose metabolism, lipid metabolism, and body weight. Some drugs affect cardiac rhythm (eg, QT interval prolongation).

Switching from a depressive phase into a manic phase (manic switching) in bipolar disorder is an important concern with antidepressants and antipsychotics. The YMRS total score and incidence of adverse events related to manic symptoms will be used for assessing the risk of manic switching. The rate of suicide is high for bipolar disorder, and prevention of suicide is one of the important aspects in the treatment of bipolar disorder. The C-SSRS [20] is a tool designed to systematically assess and track suicidal adverse events (suicidal attempts and suicidal ideation), and is able to comprehensively identify suicidal events while limiting the over-identification of suicidal behavior.

3.5 Sample size

The target number of the randomized patients is 501 (ie, 167 patients per treatment group)

Rationale

The sample size for the study has been determined by a Monte-Carlo simulation using the Statistical Analysis Software (SAS Version 9.2, SAS Institute). The sample size calculation is based on the number of patients required for the primary analysis in the intention-to-treat (ITT) population, where the primary analysis is performed on the change from baseline in the MADRS total score at Week 6. Hochberg procedure will

be utilized for the multiplicity adjustment to the multiple comparisons between each SM-13496 (20-60 and 80-120 mg/day) group and the placebo group.

A common effect size of 0.35 (ie, an intergroup difference in change from baseline of 3.5 with a standard deviation of 10) in the MADRS total score for both SM-13496 groups over placebo group was used for estimating the sample size. A sample size of 161 per group for a total of 483 patients was estimated to yield a complete power (probability of rejecting 2 null hypotheses) of 80%, with a one-sided 2.5% significance level using Hochberg procedure for multiplicity adjustment. Considering the possibility of patients who are randomized but who do not provide any post-baseline MADRS total score, the total sample size will therefore be 501 patients or 167 patients per treatment group.

The assumed effect size of 0.35 has been determined based on the PREVAIL 2 study of which study design is similar to that of the present study. In the PREVAIL 2 study, the sample size had been calculated with effect sizes of 0.39 for both SM-13496 groups (20-60 and 80-120 mg/day), and as a result, effect sizes were 0.45 for both SM-13496 groups over the placebo group on the change from baseline at Week 6 (last observation carried forward [LOCF]) in the MADRS total score. The result of the PREVAIL 2 study is shown in Table 2.

Table 2 Change from baseline in the MADRS total score at Week 6 (LOCF) – Analysis of Covariance –, Intention-to-Treat population, in the PREVAIL 2 study

	SM-13496 20-60 mg/day (N=161)	SM-13496 80-120 mg/day (N=162)	Placebo (N=162)
LS mean (SE)	-13.9 (0.80)	-13.9 (0.78)	-9.5 (0.79)
Inter-treatment difference vs. placebo (SE)	-4.5 (1.10)	-4.4 (1.10)	
Effect size	0.45	0.45	

LS means are from an analysis of covariance (ANCOVA) with treatment and pooled study site as fixed factors and baseline value as a covariate.
Effect size is the absolute value of the LS mean difference from placebo divided by the model estimate of the pooled SD (the SE of the LS Mean difference divided by the square root of the sum of inverse treatment group sizes).

To account for the limited number of placebo-controlled clinical studies in patients with depressive symptoms associated with bipolar disorder in Japan or Asia, the effect sizes for the present study were conservatively assumed. Therefore, the effect size of 0.35 for the differences of change in the MADRS total score between both SM-13496

groups and placebo group has been selected for estimating the sample size.

4. Patient population

The target population is patients with major depressive episodes associated with bipolar I disorder.

4.1 Selection of Study Population

4.1.1 Inclusion criteria

Patients who fulfill the following criteria will be included in the study. If the patient eligibility is uncertain, the investigator should discuss enrollment of the patient with a medical monitor prior to randomization.

1) Patients who were fully informed of and understand the objectives, procedures, and possible benefits and risks of the study and who provided written voluntary consent to participate in the study. If the patient is a minor at the time of consent, written consent should be obtained from a legally acceptable representative (guardian) in addition to the patient him/herself.
2) Outpatients aged 18 through 74 years at the time of consent.
3) Patients with bipolar I disorder, most recent episode depressed, with or without rapid cycling disease course ($\geq$ 4 episodes of mood disturbance but < 8 episodes in the 12 months prior to screening), and without psychotic features (diagnosed by DSM-IV-TR criteria and confirmed by the Mini International Neuropsychiatric Interview [MINI]).
4) Patients who have a history of at least one manic or mixed episode (preferably with confirmation by a reliable informant, such as a family member or caregiver).
5) Patients whose current major depressive episode is $\geq$ 4 weeks and < 12 months in duration at screening.
6) Patients with a rater-administered MADRS total score of $\geq$ 20 and a computer-administered MADRS total score of $\geq$ 20 at both screening and baseline.
7) Patients with a YMRS total score of $\leq$ 12 at both screening and baseline.
8) Patients with a negative pregnancy test at screening, when the patients are female and of childbearing potential.
9) Patients who agree to use appropriate contraception (see Section 5.6, Page 44) to prevent pregnancy in female patients and the female partners of patients, when the patients or their partners are of childbearing potential.

10) Patients whose dosage of the following concomitant drugs remains unchanged for the specified duration as follows:
   - The dose of oral hypoglycemic drugs or antihypertensive drugs remained unchanged for at least 30 days prior to screening.
   - The dose of thyroid hormone (replacement therapy) remained unchanged for at least 90 days prior to screening.
   - The dose of drugs for complications (other than the above-mentioned drugs) have been stable (within ± 25%) for at least 30 days prior to screening.
   - The content of psychotherapy and cognitive behavioral therapy remained unchanged for at least 12 weeks prior to screening.

4.1.2 Exclusion criteria

Patients who meet any of the following criteria will be excluded from the study. If the patient eligibility is uncertain, the investigator should discuss enrollment of the patient with a medical monitor prior to randomization.

1) Patients who were diagnosed as having an Axis I or Axis II disorder (DSM-IV-TR criteria) other than bipolar I disorder that is the primary focus of treatment within 3 months prior to screening.
2) Patients with a score of ≥ 4 on the MADRS item 10 (suicidal thoughts) at screening or baseline.
3) Patients with a "Yes" response to the C-SSRS item 4 (active suicidal ideation with some intent to act, without specific plan) or item 5 (active suicidal ideation with specific plan and intent) at screening (within 6 months prior to screening) or baseline.
4) Patients with imminent risk of suicide or injury to self, others, or property.
5) Patients for whom diagnostic agreement (based on the Bipolarity Index) between the investigator and Bracket (Pennsylvania, the United States), the agency for computerized diagnosis, cannot be reached.
6) Patients with a history of non-response to 6-week trial of 3 or more antidepressants (with or without concomitant use of mood stabilizers) during the current episode.
7) Patients who had been hospitalized because of a manic or mixed episode within 60 days prior to screening.
8) Patients who received monoamine oxidase (MAO) inhibitor within 21 days prior to screening.
9) Patients who received fluoxetine or a combination of olanzapine and fluoxetine within 28 days prior to screening.

10) Patients who received any depot antipsychotics (sustained-release formulation) within 90 days prior to screening.
11) Patients who received clozapine within 120 days prior to screening.
12) Patients who received electroconvulsive therapy within 90 days prior to screening.
13) Patients with a ≥ 25% reduction in the MADRS total score between screening and baseline.
14) Patients with a history of HIV seropositivity.
15) Patients with a history of alcohol/drug abuse (DSM-IV-TR criteria) within 3 months prior to screening or of alcohol/drug dependence (DSM-IV-TR criteria) within 12 months prior to screening. Exceptions include caffeine or nicotine abuse/dependence.
16) Patients with a history of hypersensitivity (eg, drug-induced anaphylaxis, rash, urticaria, or other allergic reactions) to more than one distinct chemical class of drug.
17) Patients with previous or existing clinically significant complications, such as serious nervous system, endocrine system (eg, type I diabetes mellitus), hepatic, renal, hematological, respiratory, cardiovascular (eg, unstable angina, congestive heart failure), gastrointestinal, urological, or other diseases. Patients who have a history of any of such diseases and who are considered ineligible for the study by the investigator.
18) Patients with acute hepatitis, severe chronic hepatitis or marked hepatic dysfunction. When the hepatitis screening test is positive, the investigator should evaluate carefully patient eligibility on the basis of his or her medical history or other laboratory data.
19) Patients with a gastrointestinal disease or a surgical history that may affect drug absorption, distribution, metabolism, or excretion.
20) Patients with any chronic organic disease of the central nervous system (ie, tumor, inflammation, convulsive seizure, vascular disorders, Parkinson's disease, Alzheimer's disease or other type of dementia, myasthenia gravis, or other degenerative diseases) .
21) Patients with any mental retardation or persistent neurological findings due to serious head injury.
22) Patients with a BMI of ≤ 18 kg/m^2 or ≥ 40 kg/m^2 at screening.
23) Patients with previous or existing macular or retinal pigment changes.

24) Patients with a previous (within 5 years prior to screening) or existing malignant tumor (excluding appropriately treated basal cell carcinoma of the skin, squamous cell carcinoma, and uterine cervix cancer).
25) Patients with a history of neuroleptic malignant syndrome.
26) Patients with severe tardive dyskinesia, severe dystonia, or other severe motor dysfunction.
27) Patients with an HbA1c (NGSP) value of 8.4% or higher at screening.
28) Patients with a history or presence of clinically significant ECG abnormality.
29) Patients who have received the study medication (including placebo) in a previous clinical study of SM-13496.
30) Patients who are breastfeeding.
31) Patients who are currently participating or participated in a clinical study with an investigational or marketed compound or device within 3 months prior to screening or who participated in 3 or more clinical studies within 12 months prior to screening.
32) Patients who are otherwise considered ineligible for the study by the investigator.

4.2 Method of assigning patients to treatment groups

[redacted], the Interactive Web Response System (IWRS) vender, is responsible for generating the randomization code by computer software incorporating a random number generator. The allocation ratio is 1:1:1 (20-60 mg: 80-120 mg: placebo).

4.2.1 At screening (Visit 1)

A unique subject number will be assigned to each patient who provides informed consent by the IWRS. The subject number consists of [redacted]

If a patient does not meet the study entry criteria, his or her subject number cannot be reassigned to another patient. If a patient is re-screened, he or she will receive a new subject number, which cannot be reassigned to another patient. A patient may be re-screened up to 2 times. The subject number will be used for patient identification in all procedures throughout the study.

4.2.2 At baseline (Visit 2)

The investigator will evaluate patient eligibility for the study and input it into the IWRS. The IWRS will randomly assign the eligible patient to one of the treatment groups: the 20-60 mg group, the 80-120 mg group, or the placebo group.

4.3 Discontinuation of patients from the study

4.3.1 Discontinuation criteria

Patients may be discontinued from the study treatment and assessments at any time for any of the following reasons:

- Adverse event
- Lack of efficacy
- Pregnancy
- Withdrawal by patient
- Noncompliance
- Protocol violation
- Lost to follow-up
- Other

The investigator should terminate the study treatment if a female patient becomes pregnant (see Section 7.2, Page 59) or if any adverse events or lack of efficacy results in psychotic hospitalization.

4.3.2 Procedures for discontinuation

When a patient who enters the treatment phase discontinues before study completion, the investigator should perform all applicable activities scheduled at the time of discontinuation and the follow-up assessment, and record the primary reason in the electronic case report form (eCRF). The investigator will access the IWRS and update the patient final status. The date of discontinuation is defined as the day of final administration of the study drug. The study drug unused or partially used should be returned by the patient.

If a patient discontinues the study treatment because of any AEs, the patient should be monitored until resolution or stabilization of the AE, and the investigator should perform the best possible observation, tests and evaluation as well as give appropriate treatment and take all possible measures for the safety of the patient. Any AEs that are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 6.4.1.4 (see Page 54).

4.4 Stay at the study site

An up to 24-hour period of inpatient hospitalization will be permitted, when needed, to facilitate the completion of study related assessments. Such medical hospitalization must be approved by the medical monitor on a case-by-case basis.

5. Study treatment

5.1 Study drug and comparators

5.1.1 Identity

SM-13496 20 mg tablets and placebo tablets will be used. SM-13496 20 mg tablets are white film-coated tablets containing 20 mg of lurasidone HCl. The placebo formulation will match the active drug tablets (SM-13496 20 mg) in all outward physical characteristics.

5.1.2 Packaging and labeling

5.1.2.1 Packaging

All study drugs will be packaged in 7-day supply (plus 2 days) blister cards. Each card used in the study will contain 6 columns and 9 rows. Each row will contain 6 tablets of the study drug. Depending on treatment assignment, each tablet will contain either SM-13496 (20 mg) or matching placebo.

5.1.2.2 Labeling

The blister cards of the study drug should be labeled. Labeling will include the following information basically and will be modified in accordance with the local regulations:

- Name and address of the sponsor
- Name of the study drug
- Study number
- Lot number
- Kit number
- Number of tablets
- The standard statement: "Clinical trial use only"
- Storage condition
- Expiration date

5.1.3 Storage

All study drugs should be stored under appropriate storage conditions in a secure location to which only the investigator and designated persons have access. The appropriate storage condition will be specified in the guidance for drug accountability provided by the sponsor.

5.1.4 Accountability

The study drug should be received by the principal investigator or a designated person at the study site. The study drug will be dispensed only in accordance with the protocol. The investigator or a designated person will be responsible for keeping accurate records of the study drug received from the sponsor, the amount dispensed to and returned by the patients, and the amount remaining at the conclusion of the study. At the end of the study, all study drug including unused or partially used study drug, and blister cards of used or unused study drug should be returned to the sponsor or designee after confirmation with the clinical research associate.

5.2 Treatment

5.2.1 Dosage of the study drug

The study drug administration will be initiated on the day after randomization. Patients in the 20-60 mg group will receive 20 mg of SM-13496 on Days 1 to 7 and then flexible dose of SM-13496 within a range of 20 to 60 mg for 5 weeks (starting on Day 8). Patients in the 80-120 mg group will receive 20 mg of SM-13496 on Days 1 and 2, 40 mg on Days 3 and 4, 60 mg on Days 5 and 6, 80 mg on Day 7, and then flexible dose within a range of 80 to 120 mg for 5 weeks (starting on Day 8). Patients in the placebo group will receive placebo for 6 weeks. The study drug should be administered orally within 30 minutes after evening meal once daily.

The dose can be increased or decreased by 20 mg/day at the scheduled visits from Week 1 to 5. At the scheduled visits at Week 1 or after, when no safety concerns are found and the CGI-BP-S (depression) score is within the range from 5 (markedly ill) to 7 (very severely ill), the dose should in principle be increased by 20 mg/day. When any safety concerns are raised, the dose can be reduced by 20 mg/day at unscheduled visits. Dose increases will be not permitted at unscheduled visits. At all visits after Visit 2 (Day −1, baseline), including unscheduled visits, the reason for the dose selection should be stated in the electronic case report forms (eCRFs).

5.2.2 Dispensing of study drug

The investigator or a designated person will access the IWRS for dispensing the study drug to patients at Visit 2 (Day −1, baseline), Visits 3 to 7, and unscheduled visits if necessary. At each of these visits, the IWRS will assign a kit number of a blister card that is to be dispensed to the patient. Each card will contain enough tablets for a 7-day supply, plus an additional 2-day supply. The patient should use the additional 2-day supply in the case of extension of visit interval. Patients will be instructed to

take the study drug in a blister card dispensed at Visit 2 for the first treatment week, even if the interval between Visit 2 and Visit 3 is shorter than 7 days.

5.2.3 Treatment compliance

The investigator will instruct patients to take the study drug strictly in accordance with directions and to return blister cards. Patients will be instructed to take 6 tablets (one row on a blister card) each day, according to dosing instructions. For 1 week, the reserve supply of the study drug (2 days) should only be used to extend treatment (if necessary) until the following visit. In the event that any study drug is lost or damaged, patients will be directed to contact the study site immediately for replacement instructions.

Treatment compliance will be monitored and determined at Visits 3 to 8 and at discontinuation. Compliance will be assessed by counting the number of tablets to be taken and taken actually. Noncompliance is defined as missing more than 25% of the scheduled doses or taking more than 125% of doses.

5.3 Concomitant medications and therapies

The following information of all medication administered between Visit 1 and the assessment at Visit 8 (for patients proceeding to the long-term study) or the follow-up visit (for patients not proceeding to the long-term study) will be recorded in the eCRF:

- drug name
- drug type; antipsychotics, antidepressants, mood stabilizers, anxiolytics, hypnotics, antiparkinson drugs, or other
- daily dose (for antipsychotics and mood stabilizers only)
- route of administration
- start date
- stop date
- frequency (for antipsychotics and mood stabilizers only)
- indication

Table 3 shows the restriction on concomitant medications/therapies.

Table 3 Restriction on concomitant medications/therapies

	Screening phase	Treatment phase	Follow-up
CYP3A4 inhibitors and inducers	A	A	C
Clozapine	A	A	C
Depot antipsychotics	A	A	C
MAO inhibitors	A	A	C
Other investigational products and post-marketing clinical study drugs	A	A	A
Chinese herbal medication	A	A	C
Ginkgo Biloba extract, Kava Kava, St. John's wort	A	A	C
Electroconvulsive therapy	A	A	C
Psychotropic medications (excluding antiparkinson drugs, anxiolytics, and hypnotics)	B	A	C
Medications for extrapyramidal symptoms	B	B	C
Anxiolytics	B	B	C
Hypnotics	B	B	C
Medications for complications	B	B	C
Psychotherapy and cognitive behavioral therapy	B	B	C

A, Prohibited; B, Restricted; C, No restrictions

5.3.1 Prohibited concomitant medications/therapies

The following medications and therapies will be prohibited from Visit 1 until the end of the treatment phase:

- Cytochrome P-450 enzyme 3A4 (CYP3A4) inhibitors and inducers (eg, itraconazole, fluconazole, erythromycin, beverages and foods containing grapefruit) excluding dermatologic drugs for external use
- Clozapine
- Depot antipsychotics
- MAO inhibitors
- Other investigational products and post-marketing clinical study drugs (prohibited also until the follow-up visit)
- Chinese herbal medication
- Ginkgo Biloba extract, Kava Kava and St. John's wort
- Electroconvulsive therapy

5.3.2 Restricted concomitant medications/therapies

5.3.2.1 Psychotropic medications

(1) Psychotropic medications (excluding antiparkinson drugs, anxiolytics, and hypnotics)

Psychotropic medications (eg, antipsychotics, antidepressants, mood stabilizers) excluding permitted antiparkinson drugs, anxiolytics, and hypnotics (see Items (2) to (4) in this section) will be restricted as follows:

- For patients untreated with psychotropic medication at screening, psychotropic medications will be prohibited from screening until the end of the treatment phase.
- For patients treated with any psychotropic medications at screening, the psychotropic medications should be titrated down appropriately and terminated at least 3 days before the initiation of the study treatment. Psychotropic medications will be prohibited during the treatment phase.

(2) Medications for extrapyramidal symptoms (eg, antiparkinson drugs)

Medications for extrapyramidal symptoms (eg, antiparkinson drugs) will be restricted as follows:

- For patients untreated with drugs for extrapyramidal symptoms at screening, drugs for extrapyramidal symptoms will be prohibited from screening until the initiation of the study treatment.
- For patients treated with drugs for extrapyramidal symptoms at screening, the drugs should be titrated down appropriately and terminated before the initiation of the study treatment.
- For all patients, if any extrapyramidal symptoms develop or worsen after the initiation of the study treatment, only one of the drugs listed in Table 4 may be used, within the dose range specified in the table. If the drug is not effective, the drug may be replaced by another drug among the drugs listed in Table 4. For akathisia, propranolol ($\leq$ 120 mg/day), amantadine ($\leq$ 300 mg/day), or one of the drugs listed in Table 4 may be used. If the above-mentioned drugs are not available at the study site, similar drugs at equivalent doses may be used with prior authorization of the medical monitor.
- For all patients, antiparkinson drugs and other drugs for extrapyramidal symptoms will be prohibited for prophylactic purposes.

Table 4 Permitted concomitant antiparkinson drugs

Drug	Daily dose
Biperiden	≤ 16 mg
Trihexyphenidyl	≤ 10 mg
Benztropine	≤ 6 mg
Diphenhydramine	≤ 300 mg

(3) Anxiolytics

For patients treated with any anxiolytic drugs at screening, the anxiolytic drugs should be titrated down appropriately and terminated at least 3 days before the initiation of the study treatment. Lorazepam (≤ 2 mg/day) may be used as needed, for the treatment of anxiety, agitation, irritation, and other psychiatric symptoms/signs, between screening and Week 3. However, lorazepam will be prohibited within 8 hours before the assessment of the MADRS, CGI-BP-S, SDS, YMRS, HAM-A and C-SSRS. If lorazepam is not available at the study site, similar drugs at equivalent doses may be used with prior authorization of the medical monitor. And after Week 3 until the end of the treatment phase, anxiolytics including lorazepam will be prohibited.

(4) Hypnotics

For patients treated with any hypnotics at screening, the hypnotics should be titrated down appropriately and terminated at least 3 days before the initiation of the study treatment. For insomnia, only one of the drugs listed in Table 5 may be used before bedtime between screening and Week 3. Hypnotics can be used only once per night and will be prohibited within 8 hours before the assessment of the MADRS, CGI-BP-S, SDS, YMRS, HAM-A, and C-SSRS. If the drugs listed in Table 5 are not available at the study site, similar drugs at equivalent doses may be used with prior authorization of the medical monitor. And after Week 3 until the end of the treatment phase, hypnotics including the drugs listed in Table 5 will be prohibited.

Table 5 Permitted concomitant hypnotics

Drug	Daily dose
Temazepam	≤ 30 mg
Zolpidem	≤ 10 mg
Zolpidem CR	≤ 12.5 mg
Eszopiclone	≤ 3 mg
Zaleplon	≤ 20 mg

5.3.2.2 Medications for complications

Any medications for complications used at screening will be continued during the study without any modification of the dosage unless the complications worsen or improve.

5.3.2.3 Psychotherapy and cognitive behavioral therapy

Psychotherapy, cognitive behavioral therapy, or other similar therapies that have been ongoing for at least 12 weeks before the first day of screening should be continued without any modification of the therapy contents until the end of the treatment phase. Initiation of psychotherapy or cognitive behavioral therapy will be prohibited during the study.

5.4 Blinding and unblinding

5.4.1 Methods for ensuring blinding

This is a double-blind study. Patients, investigators, persons performing the assessments, site staff, clinical operations personnel, data analysts, and personnel at the central laboratories will remain blinded to the identity of the study treatment from the time of screening until database lock and unblinding. Blinding of the study is ensured as follows:

- The assigned treatment cannot be identified through packaging and labeling.
- Drug and metabolite concentrations will not be disclosed before database lock and study unblinding.
- Serum prolactin concentration will not be disclosed before all the other data are locked.
- Week-6 efficacy (the MADRS, CGI-BP-S, SDS, YMRS, and HAM-A) will be evaluated before the initiation of study treatment in the long-term study (Study D1002002). The data will be entered into eCRFs before the patient's first assessment (Week 1) in the long-term study. The data recorded in the eCRFs may be revised only if there is a valid reason (eg, incorrect input).

5.4.2 Emergency unblinding procedures

In the case of medical emergencies when the principal investigator or an authorized delegate considers it essential to know the study treatment for immediate medical management, the principal investigator or an authorized delegate should contact the sponsor/designee or the medical monitor, if possible to discuss the reason or need for the code break prior to revealing the treatment identity.

A 24-hour code-break service will be available via the IWRS for the principal investigator. All treatment code breaks must be fully documented and signed with the time, date, reason, and name of person responsible for breaking the blind and tracked on the unblinding log. The breaking of the blind must result in the withdrawal of the patient, and the patient should return to the study site and complete the Week 6/ discontinuation assessment.

The sponsor retains the right to break the randomization code for a patient who develops any serious adverse events (SAEs) that are unexpected and are suspected to be causally related to the study drug, and that potentially require expedited reporting to regulatory authorities. The randomization codes will not be broken for the planned analyses of data until all data from each patient have been evaluated and documented.

5.5 Restrictions for patients

At Visits 2 and 8 and at discontinuation, patients should be fasting for at least 10 hours before blood sampling on the day of the scheduled visit.

5.6 Contraception

Women of childbearing potential can be enrolled. However, adequate contraception should be used throughout the study and for at least 30 days after receiving the last dose of study drug to avoid the patient or his partner becoming pregnant. Adequate contraception is defined as continuous use of either a 2-barrier method (eg, condoms and spermicide or diaphragms and spermicide), a hormonal contraceptive, or abstinence.

Acceptable hormonal contraceptives include the following: a) contraceptive implant (such as Norplant®), implanted at least 90 days prior to baseline; b) injectable contraception (such as medroxyprogesterone acetate injection) given at least 14 days before baseline; c) oral contraceptive taken as directed for at least 30 days before baseline.

Patients who are of non-reproductive potential, that is a patient who is surgically sterile, has undergone tubal ligation, or is postmenopausal (defined as at least 12 month of spontaneous amenorrhea or between 6 and 12 months of spontaneous amenorrhea with follicle stimulating hormone concentrations within postmenopausal range as determined by laboratory analysis) are not required to remain abstinent or use adequate contraception.

If a female patient has been confirmed being pregnant, the patient should immediately discontinue the study medication. If a pregnancy has been confirmed in a female patient or a female partner of patient, the investigator should follow the procedure outlined in Section 7.2 (see Page 59).

6. Measurements

Study schedule is shown in Table 1 (see Page 25). The following data will be collected.

6.1 Screening and demographic measurements

The following data will be recorded at screening:

1) Demographics
   - Date of birth, sex, race, ethnicity, height
2) Disease data
   - time of initial onset of bipolar I disorder
   - DSM-IV-TR diagnostic code (regarding severity/psychotic/remission specifiers) of the current major depressive episode
   - time of onset of the current major depressive episode
   - presence or absence of characteristics of rapid cycling disease course
   - number of mood episodes for the consequent 12 months, by episode type
   - time of onset of the most recent manic episode, hypomanic episode, and mixed episode
   - time of most recent hospital discharge if hospitalized because of manic, mixed manic or major depressive episodes
   - number of hospitalization due to bipolar I disorder
   - psychiatric disease other than bipolar I disorder; diagnosis, DSM-IV-TR diagnostic code, date of onset
3) Medical history (only clinical significant history); diagnosis, time of onset, time of remission
4) Complications; diagnosis and time of onset
5) Bipolarity Index (BPI)

   The BPI is a diagnostic instrument that considers 5 "dimensions" of bipolarity:

   1. Hypomania or mania
   2. Age of onset of first mood episodes
   3. Illness course and other features generally only apparent over time
   4. Response to medications (antidepressants and mood stabilizers)

5. Family history of mood and substance use problems

Each item is scored between 0 and 20 based on the severity of symptoms present within each category. The scale contains anchors for each dimension designed to facilitate scoring. In the study, the BPI will be administered using a computer administered interview. The results of this assessment will be used to confirm the diagnosis of bipolar 1 disorder. The data entered into the laptop computer will not be monitored, but will be attached to the study database.

Each site will be provided with a laptop computer that will record the patient's responses to the BPI computerized questionnaire. Each site will receive training on use of the laptop and perform a secure data transmission test with [redacted] During the interactive BPI interview, the computer is not connected to the Internet and the subject's access is limited to only the subject-user interface. The software places an unalterable time and date stamp on each interactive interview. The study assigned patient number is the only identifying information stored into the laptop computer and transmitted to Bracket.

After the screening visit, the site will transfer the data collected by the computer through a secure, encrypted file transfer protocol (FTP) connection. The transfer will be acknowledged to the site on the laptop screen. The data are stored on a password-protected server that restricts access to registered users or IP addresses. The patient's responses will be evaluated by clinical experts at [redacted]

Cases not meeting DSM-IV-TR criteria for bipolar I disorder, most recent episode depressed, with or without rapid cycling will not be approved by Bracket for study entry. Any diagnostic uncertainty raised by patient's responses on the BPI, must be resolved by the investigator in collaboration with Bracket in order to establish a confident diagnosis. Patients for whom diagnostic agreement between the investigator and Bracket cannot be reached are not eligible for continued study participation.

Written documentation of the independent expert's report will be provided to the site electronically or via fax. The site staff will enter the confirmation of diagnosis (based on the BPI) in the eCRF.

6) Mini International Neuropsychiatric Interview (MINI)
The MINI is a short structured diagnostic interview, developed for DSM-IV-TR psychiatric disorders, designed to meet the need for a short but accurate structured psychiatric interview for multicenter clinical trials and epidemiology. Raters at the study site will assess the MINI (version 6.0 10/10/10) after the BPI. The MINI will be utilized to identify other exclusionary psychiatric diagnoses..
7) Hepatitis screening; HBs antigen, HCV antibody (Low positive HCV antibody will be confirmed by INNO-LIA method.)

6.2 Efficacy measurements

6.2.1 Montgomery-Åsberg Depression Rating Scale (MADRS)

The MADRS [11] is a clinician-rated assessment of the patient's level of depression. The measure contains 10 items; apparent and reported sadness, inner tension, reduced sleep and appetite, difficulty concentrating, lassitude, inability to feel, and pessimistic and suicidal thoughts. Each item is scored in a range of 0 to 6 points, with higher scores indicating increased depressive symptoms. The Structured Interview Guide for the MADRS (SIGMA) [21] will be used for the MADRS assessment.

A qualified rater at the site will assess the MADRS at Visits 1 to 8 and at discontinuation. The assessment at Visit 8 or at discontinuation should be performed within 72 hours after the final administration of the study drug and before the initiation of post treatment with antipsychotics, psychotropic drugs or the study drug in the long-term study. The rater should receive specific training for the MADRS assessment provided by the sponsor and will be required to be certified by the sponsor before his or her initial assessment of the MADRS.

The MADRS scores from this assessment will be entered into the eCRF. These scores will also be entered on a laptop computer issued by [redacted] at the site. In addition to MADRS administration by a qualified site rater, each patient will complete an interactive depressive symptom interview on the laptop computer after completion of the rater assessment. The data entered into the laptop computer will not be monitored, but will be attached to the study database.

The interview will involve a series of probe and follow up questions with multiple-choice response options. Data from the self-report computer-based depressive symptom interview will be compared to data derived from the site rater interview (entered into the laptop computer) on an ongoing basis as part of a remote

rater management (RRM) program that will be conducted by [redacted] RRM allows the study team to monitor the primary outcome measure at treatment phase assessments in the study and provide ongoing feedback and remediation to the rater in the study, when necessary.

Each study site will be provided with a laptop computer containing the RRM software, receive training on use of the laptop, and perform a secure server connection test with the central vendor. The laptop is not connected to the Internet during the interactive interview. The RRM software restricts the user's access to only the subject-user interface. The RRM software places an unalterable time and date on each report which cannot be modified. The study assigned subject ID number is the only identifying information that is stored into the laptop computer and transmitted to the vendor; therefore, the vendor will be blinded to the study treatment.

6.2.2 Clinical Global Impression: Bipolar Version - Severity of Illness (CGI-BP-S)

The CGI-BP-S [14] is a clinician-rated assessment of the patient's current illness state on a 7-point scale, where a higher score is associated with greater illness severity. Following a clinical interview, the CGI-BP-S can be completed in 1 to 2 minutes. A qualified rater at the site will assess the CGI-BP-S at Visits 1 to 8 and at discontinuation. The assessment at Visit 8 or at discontinuation should be performed within 72 hours after the final administration of the study drug and before the initiation of post treatment with antipsychotics, psychotropic drugs or the study drug in the long-term study.

6.2.3 Sheehan Disability Scale (SDS)

The SDS [15] is a composite of 3 self-rated items designed to measure the extent to which 3 major sectors in the patient's life are impaired by depressive symptoms. This anchored visual analog scale uses spatiovisual, numeric, and verbal descriptive anchors simultaneously to assess disability across three domains: work, social life, and family life. At Visits 2 and 8 and at discontinuation, the patient rates the extent to which his or her (1) work, (2) social life or leisure activities, and (3) home life or family responsibilities are impaired by his or her symptoms on a 10-point visual analog scale. The assessment at Visit 8 or at discontinuation should be performed within 72 hours after the final administration of the study drug and before the initiation of post treatment with antipsychotics, psychotropic drugs or the study drug in the long-term

study. There are verbal descriptors for the points on the scale as well as numerical scores that provide more precise levels of the verbal descriptors.

6.2.4 Young Mania Rating Scale (YMRS)

The YMRS [16] is an 11-item instrument used to assess the severity of mania in patients with a diagnosis of bipolar disorder. The 11 items are: elevated mood, increased motor activity energy, sexual interest, sleep, irritability, speech (rate and amount), language-thought disorder, content, disruptive-aggressive behavior, appearance and insight. The YMRS is a clinician-rated assessment. The YMRS uses operationally-defined anchor points. Ratings are based on patient self-reporting, combined with clinician observation (accorded greater score). The Concordant YMRS Structured Interview Guide will be used for the YMRS assessment.

A qualified rater at the site will assess the YMRS at Visits 1 to 8 and at discontinuation. The assessment at Visit 8 or at discontinuation should be performed within 72 hours after the final administration of the study drug and before the initiation of post treatment with antipsychotics, psychotropic drugs or the study drug in the long-term study. The rater should receive specific training for the YMRS assessment provided by the sponsor and will be required to be certified by the sponsor before his or her initial assessment of the YMRS.

6.2.5 Hamilton Rating Scale for Anxiety (HAM-A)

The HAM-A [17] is a rating scale developed to quantify the severity of anxiety symptomatology. It consists of 14 items, each defined by a series of symptoms. Each item is rated on a 5-point scale, ranging from 0 (not present) to 4 (severe/disabling). The Structured Interview Guide for the HAM-A (SIGH-A) will be used for the HAM-A assessment. A rater at the site will assess the HAM-A at Visits 2 and 8 and at discontinuation. The assessment at Visit 8 or at discontinuation should be performed within 72 hours after the final administration of the study drug and before the initiation of post treatment with antipsychotics, psychotropic drugs or the study drug in the long-term study.

6.3 Pharmacokinetic measurements

Serum concentrations of SM-13496 and its metabolites will be determined in only patients who provide informed consent for blood sampling for pharmacokinetics. To maintain the blind, the laboratory ([redacted]) will report the serum concentration data to the sponsor after unblinding the treatment code.

1) Measurement
Serum concentration of SM-13496 and its major metabolites (hydroxylated products [ID-14283 and ID-14326], cleaved product [ID-11614])

2) Blood sampling
At Visits 5, 6 and 8, and at discontinuation (if after Week 3), 10 mL of blood will be collected from a vein at 13 to 15 hours after the administration of the study drug.

3) Recording
The following information will be recorded in eCRFs: date and time of blood sampling, time of taking the study drug on the day before the sampling.

6.4 Safety measurements

6.4.1 Adverse events

6.4.1.1 Definitions

The definitions of adverse events (AEs) and serious adverse events (SAEs) are shown below. It is of the utmost importance that all staff members involved in the study are familiar with the content of this section. The principal investigator will be responsible for ensuring that all site staff have read and understand this content.

Adverse events (AEs)

An adverse event (AE) is any untoward medical occurrence in a patient treated with a medicinal (investigational) product and which does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease occurring after the administration of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. AEs may include the onset of new illness and the exacerbation of pre-existing conditions.

Lack of efficacy may be an expected potential outcome and should not be reported as an adverse event unless the event is unusual in some way.

The investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE and not the individual signs/symptoms.

Serious adverse events (SAEs)

A serious adverse event (SAE) is an AE that meets one or more of the following criteria:

- Results in death.
- Is life-threatening (ie, a patient is at immediate risk of death at the time of the event, not an event where occurrence in a more severe form might have caused death).
- Requires hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event that may jeopardize the patient or may require a medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization.

The term "severe" is often used to describe the severity of a specific event (as in mild, moderate, or severe myocardial infarction) (see Section 6.4.1.3, Page 52); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning as defined by the criteria above.

During the study, if a patient has a hospitalization or procedure (eg, elective surgery) that was scheduled before the study entry, ie, before informed consent for an event/condition that occurred before the study, the hospitalization is considered a therapeutic intervention and not the result of a SAE. However, if the event/condition worsens during the study, it should be reported as an AE (or SAE, if the event/condition results in a serious outcome such as prolongation of hospitalization).

Life-threatening means that the patient was, in the view of the investigator, at immediate risk of death from the event as it occurred. This definition does not include an event that had it occurred in a more severe form might have caused death.

6.4.1.2 Objective findings

Clinically significant abnormal objective findings (eg, clinical laboratory value, ECG value, and physical examination observation) will also be recorded as AEs.

When a clear diagnosis is available that explains the objective findings, this diagnosis will be recorded as the AE, and not the abnormal objective finding (eg, viral hepatitis will be recorded as the AE, not transaminase elevation). If a definite diagnosis is not available, then record the sign (eg, clinically significant elevation of transaminase levels) or symptom (eg, abdominal pain) as the AE.

Clinical laboratory test results will be reviewed by the investigator. The investigator should determine the clinical significance of all out of range values. Clinical laboratory test with possibly drug-related or clinically relevant abnormal values of uncertain causality may be repeated. Any abnormal values that persist should be followed at the investigator's discretion.

All on-site ECG tracings and ECG reports by the ECG parameter measurement center will be reviewed by the investigator. The investigator should determine the clinical significance of all abnormal ECGs. ECG with possibly drug-related or clinically relevant abnormal findings of uncertain causality may be repeated. Any abnormal ECGs that persist should be followed at the investigator's discretion.

6.4.1.3 Collection and recording of adverse events

AEs will be collected for each patient from the time the informed consent is obtained until the last study visit. Patients should be queried in a non-leading manner, without specific prompting (eg, "Has there been any change in your health status since your last visit?"). AEs and SAEs will be monitored throughout the study at all visits.

All AEs should be collected and recorded in the patient's study records/source documents, in accordance with the investigator's normal clinical practice, and in the eCRFs.

Each AE will be evaluated for duration, severity, seriousness, action taken with the study treatment, outcome, and causal relationship to the study treatment. Definitions for severity, action taken with the study treatment, outcome, and causal relationship to the study treatment are presented below. When the severity of an AE which has an onset before the treatment phase worsens after the initiation of the treatment phase, the more severe AE should be captured as a new AE.

Severity of AE

- **Mild** – Ordinarily transient symptoms that do not influence performance of patient's daily activities. Other treatment is not ordinarily indicated.
- **Moderate** – Marked symptoms sufficient to make the patient uncomfortable. Moderate influence on performance of patient's daily activities. Other treatment may be necessary.
- **Severe** – Symptoms cause considerable discomfort. Substantial influence on patient's daily activities. May be unable to continue the study, and other treatment may be necessary.

When the severity of an AE changes, the maximum severity for the event should be noted.

The action taken with the study treatment:

- **Drug Withdrawn** – Study drug stopped permanently.
- **Dose Reduced**
- **Dose Increased**
- **Dose Not Changed**
- **Not Applicable**

The outcome of the AE:

- **Recovered/Resolved**
- **Recovering/Resolving**
- **Not Recovered/Not Resolved**
- **Recovered/Resolved with Sequelae**
- **Fatal**
- **Unknown**

The causal relationship of the AE to the study treatment:

- **Not related**
  - **Not related** – Improbable temporal relationship and is plausibly related to other drugs or underlying disease.
  - **Unlikely** – occurred within a reasonable time frame after administration/discontinuation of the study drug, but there is a likely association of an intercurrent/underlying medical condition or other drugs.

- **Related**
  - **Possible** – occurred in a reasonable time after study drug administration, but could be related to concurrent drugs or underlying disease.
  - **Probable** – occurred in a reasonable time after study drug administration, is unlikely to be attributable to concurrent drugs or underlying disease, and there is a plausible mechanism to implicate the study drug.
  - **Definite** – occurred in a reasonable time after study drug administration and cannot be explained by concurrent drugs or underlying disease. The AE should respond to dechallenge/rechallenge, however, this is not mandatory before assigning a definite causality.

The medical monitor is the initial contact person for protocol related questions or discussion of AEs.

6.4.1.4 Follow-up of AEs

Appropriate measures should be taken as necessary to treat AEs, and the response of the patient should be monitored as medically appropriate, as well as recorded. Clinical laboratory and diagnostic measures should be obtained as needed.

All AEs will be followed until resolution, stabilization of the condition, the event being otherwise explained, or the patient being lost to follow-up.

6.4.2 Laboratory tests

Blood and urine samples for the laboratory test will be collected at Visits 1, 2, 3, 6, 8, and at discontinuation, and will be submitted to the central laboratory for analysis. At Visit 8 or at discontinuation, the samples should be collected within 72 hours after the final administration of the study drug and before the post treatment with antipsychotics. At Visits 2 and 8 or at discontinuation, blood samples will be collected in a fasting condition. Collection and handling of blood samples will be performed in accordance with the routine procedures and the separately provided instructions.

The central laboratory will analyze the samples for the tests listed in Table 6.

Table 6 Contents of the laboratory variables

Hematology	Red blood cell count, white blood cell count, hemoglobin, hematocrit, platelet count, white blood cell classification (ie, neutrophils, eosinophils, basophils, monocytes, and lymphocytes)
Blood chemistry test	AST, ALT, ALP, γ-GTP, total protein, total bilirubin, BUN, creatinine, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, LDH, CK, blood glucose, uric acid, HbA1c, glycoalbumin, prolactin, albumin, insulin, electrolytes (Na, K, Cl),
Endocrine	Thyroid stimulating hormone (TSH), free thyroxine (FT4), total and free testosterone
Hepatitis	HBs antigen, HCV antibody (Low positive HCV antibody will be confirmed by INNO-LIA method.)
Urinalysis (qualitative tests)	Protein, glucose, urobilinogen, occult blood

Prolactin, HbA1c (NGSP), glycoalbumin, blood glucose, total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides will be measured only at Visits 1, 2 and 8 and at discontinuation. Blood glucose will be measured in fasting condition at Visits 2 and 8 and at discontinuation.
TSH, FT4, and total and free testosterone will be measured only at Visits 1 and 8 and at discontinuation.
Hepatitis tests will be performed only at screening.

The prolactin concentration data will not be disclosed until all the other data is locked to ensure the study blindness, as antipsychotics often increase prolactin concentrations, and will be reported to the investigators and the sponsor.

Pregnancy test (urine chorionic gonadotropin) will be performed in female patients of childbearing potential before menopause at the study site at Visits 1 and 8 and at discontinuation. If urine pregnancy test is positive, serum pregnancy test will be performed.

Total and free testosterone will be measured only in male patients.

6.4.3 Vital signs

Body temperature, pulse rate and systolic and diastolic blood pressure (sitting) will be measured at Visits 1 to 8 and at discontinuation. Body weight will be measured at Visits 1, 2, and 8, and at discontinuation. The measurements at Visit 8 or at discontinuation should be performed within 72 hours after the final administration of the study drug and before the initiation of post treatment with antipsychotics.

6.4.4 12-lead Electrocardiography (ECG)

At Visits 1, 2, and 8 and at discontinuation, a 12-lead ECG will be performed on the patients at rest. The test at Visit 8 or at discontinuation should be performed within 72 hours after the final administration of the study drug and before the initiation of post treatment with antipsychotics. The electrocardiogram will be sent electronically to the ECG parameter measurement center. The cardiologist in the center will assess the electrocardiogram and measure the following ECG parameters: RR interval, QT interval, PR interval, QRS interval, and QTc (QTc Fridericia [QTcF] and QTc Bazett [QTcB])

The center will report the ECG findings and parameters to the investigator and the sponsor. The investigator will assess the ECG findings and use them for the assessment of AEs.

6.4.5 Drug-Induced Extrapyramidal Symptom Scale (DIEPSS)

The DIEPSS [18] is a clinician-rated assessment of extrapyramidal symptom induced by antipsychotics and consists of eight individual parameters; gait, bradykinesia, sialorrhea, muscle rigidity, tremor, akathisia, dystonia, and dyskinesia; and one global assessment; overall severity. The severity of each item is graded 0 (normal) to 4 (severe). The investigator will assess the DIEPSS at Visits 2 to 8 and at discontinuation. The assessment at Visit 8 or at discontinuation should be performed within 72 hours after the final administration of the study drug and before the initiation of post treatment with antipsychotics or the study drug in the long-term study.

6.4.6 Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS [20] is a tool designed to systematically assess and track suicidal adverse events (suicidal behavior and suicidal ideation) throughout the study. The C-SSRS can comprehensively identify suicidal events and limit the over-identification of suicidal behavior. The rater will assess the C-SSRS at Visits 1 to 8 and at discontinuation. The 'baseline/screening' version will be used at Visit 1 and the 'since last visit' version at Visits 2 to 8 and at discontinuation. The assessment at Visit 8 or at discontinuation should be performed within 72 hours after the final administration of the study drug and before the initiation of post treatment with antipsychotics or the study drug in the long-term study. The rater should receive specific training before his or her initial assessment of the C-SSRS.

6.4.7 Total volume of blood sampling

The total volume of blood to be drawn from each patient is shown in Table 7.

Table 7 Volume of blood sampling from each patient

		Sample volume (mL)	No. of samples	Total volume (mL)
Hematology		2	5	10
Blood chemistry, TSH, FT4, hepatitis	(Visit 1)	11.5	1	11.5
	(Visit 2)	8	1	8
	(Visits 3 and 6)	3.5	2	7
	(Visit 8)	10	1	10
Total and free testosterone (male only)		10	2	20
SM-13496 serum concentration (option)		10	3	30
Total (including option)				96.5 (male) 76.5 (female)

6.5 Recommended sequence of clinical assessments

It will be recommended that the assessments are conducted in the following sequence. The unnecessary assessments will be skipped.

1) BPI
2) MINI
3) MADRS (site rater)
4) MADRS (computer administered)
5) C-SSRS
6) HAM-A
7) YMRS
8) SDS
9) DIEPSS
10) CGI-BP-S

7. Immediately reportable events

The following medical events must be immediately reported to the Sponsor:

- SAE
- Pregnancy
- Overdose

7.1 SAE

The investigator must inform the sponsor or designee of any SAEs that occur during the course of the study within 24 hours of the investigator becoming aware of the SAE by facsimile. Following the end of patient participation in the study, the investigator should report SAEs "spontaneously" to the sponsor if considered at least possibly related to the study drug. The SAE report should include the following information:

1) Study number (ie, D1002001)
2) Subject number
3) Sex
4) Date of birth
5) Name of investigator and study site
6) Nature of SAE
7) Criterion for classification as "serious"
8) Date of initial administration of the study drug
9) Start date of SAE
10) Causality assessment (if sufficient information is available to make this classification)
11) History of any ADRs
12) Relevant special conditions of the patient
13) History of the current disease and treatment for the disease
14) Details of the SAE
15) Treatment for the SAE
16) Details of study treatments
17) Details of concomitant medications
18) Details on course of the SAE
19) If the patient died, date of death, cause of death, relation between the SAE and death, anatomic findings (if available)

As a minimum requirement for the first report, information on (1) to (10) described above should be provided. The principal investigator should report available information in writing within 7 calendar days after the first reporting (this procedure is not mandatory in the case that the principal investigator has already submitted the first report, including all necessary information listed above). The principal investigator should report other necessary information not included in the first and second reports in writing as it becomes available. The sponsor may request additional information if necessary.

SAEs should be recorded in the eCRFs and the data recorded should match that on the SAE form.

In accordance with applicable law(s) and regulation(s), the sponsor or designee will promptly notify all the study sites and investigators of a SAE that is determined to be expedited to the regulatory authorities. These SAEs must be promptly reported to the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) by the principal investigator or the appropriate person at the site.

7.2 Pregnancy

Pregnancies that occur from the time that informed consent is signed through the follow-up visit will be collected and reported on the Pregnancy Event Form.

If a patient becomes pregnant during the course of the study, she will be instructed to discontinue the study medication immediately. Further, the patient (or female partner of male patient) will be instructed to return promptly to the study site and undergo a serum pregnancy test, as confirmation of pregnancy (the female partner of male patient will be asked to sign a consent form to undergo the test beforehand). If positive, the pregnant will no longer receive any additional study medication. Further, the pregnant (patient or female partner of male patient) will be asked to sign a consent form to allow the sponsor to follow her pregnancy. All pregnancies will be followed until resolution (ie, termination [voluntary or spontaneous] or birth).

The investigator must inform a pregnancy of the sponsor or designee within 24 hours of the investigator becoming aware of the pregnancy. As a minimum requirement for the first report, the following information should be provided by facsimile.

1) Study number (ie, D1002001)
2) Subject number
3) Person who is pregnant (ie, study patient or partner of male patient)
4) Date of birth of the pregnant
5) Name of investigator and study site
6) Date of initial administration of the study drug
7) Date pregnancy confirmed by HCG assay
8) Current pregnancy status

The investigator should complete the Pregnancy Event Form and sent it within 7 calendar days after the first reporting (this procedure is not mandatory in the case that

the principal investigator has already submitted the Pregnancy Event Form for the first report). The sponsor will provide the Pregnancy Event Form.

If the patient received blinded study medication, unblinding of the study medication will be offered to the patient when knowledge of such treatment may have an impact on further treatment decisions. Otherwise, information regarding what treatment the patient was assigned may be provided when the study has completed.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication.

7.3 Overdose

An overdose of the study drug will be collected and reported on the SAE Report Form. When a patient takes over 6 tablets of study drug at one time, the investigator should inform the overdose of the sponsor or designee within 24 hours of the investigator becoming aware of the overdose. As a minimum requirement for the first report, the following information should be provided by facsimile.

1) Study number (ie, D1002001)
2) Subject number
3) Sex
4) Date of birth
5) Name of investigator and study site
6) Date of initial administration of the study drug
7) Details of overdose
8) Date of overdose

The investigator should complete the SAE Report Form and sent it within 7 calendar days after the first reporting (this procedure is not mandatory in the case that the principal investigator has already submitted the SAE Report Form for the first report).

Overdose itself is not regarded as an AE. If a SAE accompanies an overdose, the SAE should be reported simultaneously (see Section 7.1, Page 58).

8. Quality management

8.1 Monitoring

The study will be monitored at all stages of its development by clinical research associates who are employed by the sponsor or its representative. Monitoring will be performed in order to confirm that the investigator and other study personnel at the study site are adhering to the study protocol, ICH GCP and local regulations.

The investigator and appropriate personnel may be requested to attend meetings or workshops that are organized by the sponsor in order to ensure acceptable protocol execution.

8.2 Data verification

The sponsor or its representative will perform source data verification in order to confirm completeness, clarity, and consistency with the source documents that are available for each patient. This will be done by comparing data in the eCRFs with the patient's medical records (original documents, data, and records). The investigator will be required to store all source documents.

For the study, original data recorded in the eCRFs and can be regarded as source data are as follows:

- Presence or absence of characteristics of rapid cycling disease course
- DSM-IV-TR diagnostic code
- Reasons why the dose is not increased regardless of the dose modification guideline and reasons for dose modification
- Outcome, severity, seriousness, and causality of AEs
- Indication of concomitant medications
- Reason for early discontinuation of the patient

Monitoring, including source data verification, should be performed routinely before the principal investigator electronically signs the eCRFs.

8.3 Audits and inspections

The study may be subject to audit by the sponsor or inspection by regulatory authorities. The investigator should accept and cooperate with the monitoring and audit by the sponsor (or its representative), and accept inspection by the IRB/IEC or regulatory authorities. All study documents including raw data should be available for direct access to source data at the request of the monitor and the auditor of the

sponsor (or its representative), the IRB/IEC, or regulatory authorities. The investigator should contact the sponsor immediately if contacted by a regulatory authority about an inspection at his or her study site.

8.4 Training of staff

The principal investigator will maintain records of all individuals involved in the study (medical, nursing and other staff). The principal investigator will ensure that appropriate training relevant to the study is provided to all of these staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

8.5 Data management

8.5.1 Electronic case report form (eCRF)

The study data of patients who provide informed consent will be captured in the eCRFs through the electronic data capture (EDC) system. The users of this system should receive training on the EDC from the sponsor or its delegate.

The data will be entered in the eCRFs according to the guidance for eCRF completion provided separately by the sponsor. The data will be recorded in the eCRFs in English as soon as data are available for entry. The investigator will record the assessment results of the MADRS, CGI-BP-S, SDS, YMRS, and HAM-A, and the date in the patient's medical document with his or her signature. Especially for patients who proceed to the long-term study (Study D1002002), at Week 6, the data should be entered in the eCRFs before the patient's first assessment (Week 1) in the long-term study. The data recorded in the eCRFs may be revised only if there is a valid reason (eg, incorrect input). After source data verification, all data will be validated by the sponsor or its representative. Missing or inconsistent data will be clarified by the investigator using the EDC system.

After confirming the entered data, the principal investigator will electronically sign the eCRFs to verify the accuracy of all data contained in the eCRFs. The electronic signature will be equivalent to the handwritten signature.

The sponsor will provide copies of the original eCRFs for the principal investigator, and he or she will keep them.

8.5.2 Coding

Medical histories, complications, and AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) by the sponsor. Medications will be coded using the World Health Organization (WHO) Drug Dictionary.

9. Statistical analysis

9.1 Statistical analysis plan

A statistical analysis plan will provide details on the statistical methods planned for the study and will be finalized before the unblinding of the study. If any changes are made to the statistical analysis proposed below after the study initiation, the changes to the plan will be listed along with the reason in the statistical analysis plan.

9.2 Analysis population

The primary efficacy analysis will be performed in the intention-to-treat (ITT) population. The efficacy analysis on the primary variable will be performed also in the per-protocol (PP) population for sensitivity analysis. The safety analysis will be performed on the safety population. The ITT analysis will be performed using the assigned treatment groups, and safety analysis using the groups of the treatment actually received.

9.2.1 Intention-to-treat population (ITT)

The ITT population will consist of all patients who fulfill the following conditions:

- Patients who are randomized and take at least one dose of the study drug in the treatment phase, regardless of any protocol deviations
- Patients who have baseline and at least one post-baseline evaluable the MADRS total score

9.2.2 Per-protocol population (PP population)

The PP population will consist of patients of the ITT population who fulfill the following conditions:

- Patients who fulfill the inclusion criteria (3) to (7), and (10) (see Section 4.1.1, Page 32) and do not meet any of the exclusion criteria (1), (5) to (12), (18) to (21), and (28) (see Section 4.1.2, Page 33)
- Patients who have been treated for 14 days or longer
- Patients who receive 75% to 125% of study treatment in the treatment phase
- Patients who do not receive any psychotropic medication other than

antiparkinson drugs, anxiolytics, and hypnotics during the treatment phase
- Patients who have no important protocol deviations as determined by a blinded data review

9.2.3 Safety population

The safety population will consist of all patients who are randomized and receive at least one dose of the study drug in the treatment phase.

9.3 Handling of data

9.3.1 Day 1

Day 1 is defined as the first day when the patient takes the study drug.

9.3.2 Analysis visits, baseline, and post-baseline measures

All data will be organized and analyzed according to the scheduled timing as outlined in Table 1 (see Page 25) and according to the visit denoted on the eCRFs. Unscheduled visits will not be used for analyses unless otherwise specified. The baseline data for statistical analyses will be defined as the last non-missing data on or before Day 1. Post-baseline data for statistical analysis will be defined as the non-missing data on or after Day 1 and through 7 days after the final administration of the study drug in the treatment phase (excluding baseline). The data collected at discontinuation visit will be mapped to the next scheduled visit of the actual discontinuation date.

9.3.3 Missing data

For the rating scales that consist of more than one item, if any item is missing, then the total score will be handled as missing also. The primary method for handling of missing data will be the mixed model for repeated measurements (MMRM) without explicit imputations for missing data. The LOCF method will be used for a sensitivity analysis. The final post-baseline data will be carried forward and will be defined as the Week 6 (LOCF).

9.4 Demographics and other baseline characteristics

Demographics and baseline characteristics will be summarized by treatment group for all the analysis populations. Prior and concomitant medications will be summarized by treatment group for the ITT population. Exposure to the study drug will be summarized by treatment group for the safety population.

9.5 Efficacy analysis

9.5.1 Hypothesis

Let $\mu_{20\text{-}60}$, $\mu_{80\text{-}120}$, and $\mu_{placebo}$ represent the mean changes from baseline in the MADRS total score at Week 6 in the 20-60 mg, 80-120 mg, and placebo groups, respectively. The following 2 hypotheses will be tested to compare the mean changes at Week 6 of each SM-13496 group with that of the placebo group:

- H_{01}: $\mu_{20\text{-}60} = \mu_{placebo}$ versus the alternate H_{11}: $\mu_{20\text{-}60} \neq \mu_{placebo}$.
- H_{02}: $\mu_{80\text{-}120} = \mu_{placebo}$ versus the alternate H_{12}: $\mu_{80\text{-}120} \neq \mu_{placebo}$.

9.5.2 Primary analysis

The primary efficacy variable is the change from baseline in the MADRS total score at Week 6 for testing superiority of SM-13496 (20-60 or 80-120 mg/day) to placebo. The rater-administered MADRS data will be used for all statistical analyses. The MMRM method will be used in the ITT population. The MMRM model will include treatment as a categorical factor, visit (Week 1, 2, 3, 4, 5, and 6; as a categorical variable), pooled center, the MADRS total score at baseline as a covariate, and the treatment-by-visit interaction. An unstructured covariance matrix will be used for the within-patient correlation and the Kenward-Rogers approximation will be used to calculate the denominator degree of freedom. In the case of a convergence problem with the unstructured covariance matrix, the following structures with robust sandwich estimator for the standard error of the fixed effect estimates will be assessed in a sequential fashion: heterogeneous Toeplitz, heterogeneous first-order autoregressive, and Toeplitz. Among these 3 covariance structures, the first structure yielding convergence will be used for the MMRM analysis. P-values for comparisons of primary efficacy variable at Week 6 between SM-13496 groups and the placebo group will be adjusted for multiplicity using a Hochberg procedure.

A sensitivity analysis for the primary efficacy variable will be performed using an analysis of covariance (ANCOVA) model on the ITT population. The response variable for the model will be the change from baseline in the MADRS total score at Week 6 (LOCF). The ANCOVA model will include treatment as a categorical factor, pooled study site and the MADRS total score at baseline as a covariate. The MMRM and LOCF ANCOVA analysis will also be performed on the PP population to obtain additional information on the robustness of results.

The mean change from baseline in the MADRS total score will be plotted by visit of discontinuation to assess whether there are dropout patterns that appear to violate the missing at random (MAR) assumption, which the MMRM is based upon.

Study sites with small number of patients will be pooled for the analyses. The strategy for pooling sites will be provided in the statistical analysis plan.

9.5.3 Secondary analysis

The following analysis methods will be used for secondary analyses to evaluate the efficacy of SM-13496 (20-60 and 80-120 mg/day) compared with that of placebo using the ITT population. The secondary variables are as follows:

a) Change from baseline in the CGI-BP-S score (depression) at Week 6
b) Change from baseline in the SDS total score at Week 6
c) Change from baseline in the YMRS total score at Week 6
d) Change from baseline in the HAM-A total score at Week 6
e) Change from baseline in the MADRS total score at each scheduled assessment
f) Change from baseline in the CGI-BP-S (depression) score at each scheduled assessment
g) Proportion of patients who achieve a $\geq$ 50% reduction from baseline in the MADRS total score at Week 6 (LOCF) (ie, treatment response)
h) Proportion of patients who achieve a MADRS total score of $\leq$ 12 at Week 6 (LOCF) (ie, symptom remission)

The change from baseline in the secondary variables a), c), e), and f) will be analyzed using the MMRM method described above for the primary efficacy variable. The secondary variables a) and c) will also be analyzed using the LOCF ANCOVA method described above for the primary efficacy variable, as a sensitivity analysis. The secondary variables b) and d) will be analyzed using the LOCF ANCOVA method described above for the primary efficacy variable.

For the secondary variables g) and h), a logistic regression will be performed with the 0-1 responder indicator as a dependent variable, treatment as a categorical factor, pooled study site, and the MADRS total score at baseline as a covariate, for the comparisons between each SM-13496 (20-60 and 80-120 mg/day) group and placebo group.

9.5.4 Subgroup analysis

Subgroup analysis will be performed for the change from baseline in the MADRS total score and the CGI-BP-S (depression) score at Week 6. Subgroups will include country, sex, age, and bipolar I diagnosis subtype (rapid cycling and non-rapid cycling). Inferential analysis of treatment-by-subgroup interaction at Week 6 will be performed for each subgroup variable using the MMRM method on the ITT population. The model will include treatment, visit, baseline data, pooled study site, subgroup, treatment-by-subgroup, treatment-by-visit, visit-by-subgroup, and treatment-by-subgroup-by-visit interactions. However analysis for country will be conducted using the MMRM method described above for the primary efficacy variable on the ITT population.

9.6 Pharmacokinetic analysis

The serum concentration of SM-13496 and its metabolites (hydroxylated products [ID-14283 and ID-14326], and cleaved product [ID-11614]) will be summarized and plotted by treatment group, dose, and country.

9.7 Safety analysis

9.7.1 Adverse events

The summary of AEs will be limited to treatment-emergent AEs (TEAEs), which are defined as AEs with onset on or after Day 1. An ADR will be defined as an AE related to the study treatment; an AE of which causality with study drug is related, probably related or possibly related.

The number and percentage of patients with at least one AE or ADR for each preferred term and system organ class will be summarized by treatment group. This summary will be repeated for death, SAEs, AEs leading to the study discontinuation, severe AEs, and extrapyramidal AEs.

9.7.2 DIEPSS

The change from baseline in the DIEPSS total score (excluding overall severity) and the individual DIEPSS scores will be analyzed using the MMRM method described above for the primary efficacy variable. The change from baseline in the DIEPSS total score will also be analyzed using the LOCF ANCOVA method described above for the primary efficacy variable, as a sensitivity analysis.

9.7.3 C-SSRS

The number and percentage of patients with suicidality will be summarized by treatment group, where suicidality is defined as having at least one occurrence of suicidal ideation or at least one occurrence of suicidal behavior. The numbers and percentages of patients with suicidal ideation and suicidal behavior will be summarized by treatment group.

9.7.4 Treatment-emergent mania

Number and percentage of patients with treatment-emergent mania, assessed by a YMRS total score of ≥ 16 at 2 or more consecutive assessments or with adverse reactions related to mania symptoms will be summarized by treatment group.

9.7.5 Concomitant medications

Number and percentage of patients with concomitant use of antiparkinson medication will be summarized by treatment group.

9.7.6 Laboratory tests, vital signs, body weight, and 12-lead ECG

Summary statistics for laboratory tests, vital signs, body weights, and 12-lead ECG parameters will be provided by treatment group. Continuous variables will be summarized using descriptive statistics of number of patients, mean, median, standard deviation, minimum, and maximum values. Categorical variables will be reported as frequencies and percentages. Laboratory tests as a categorical variable will be reported for shift tables. A rank ANCOVA method with adjustments for baseline value will be applied to change from baseline to Week 6 (LOCF) in serum prolactin, fasting blood glucose, HbA1c (NGSP), glycoalbumin, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, and body weight for comparison between each SM-13496 (20-60 and 80-120 mg/day) group and the placebo group.

Laboratory data will be summarized by the flagging of abnormal values in data listings. The incidence of markedly abnormal post-baseline laboratory values (MAPLV), markedly abnormal post-baseline vital signs (MAPVS), and prolonged QTc will be summarized by treatment group. In these analyses, post-baseline laboratory test values obtained at unscheduled visits will be taken into consideration.

9.7.7 Subgroup analysis

Subgroup analysis will be performed for AEs and changes from baseline at Week 6 (LOCF) in the DIEPSS total score (excluding overall severity), serum prolactin, fasting

blood glucose, HbA1c (NGSP), glycoalbumin, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, body weight, and ECG parameter (QTc). Subgroups will include sex, age and country.

9.8 Interim Analysis

Interim analysis is not planned.

9.9 Multiplicity considerations

A Hochberg procedure will be used to control the overall Type I error at 5% by taking into account multiple dose regimens for primary efficacy analysis.

10. Patient information and consent

10.1 Preparation and revision of the informed consent form

The principal investigator will prepare the informed consent form (ICF) for his/her site based on the master ICF prepared by the sponsor and investigator's brochure. The principal investigator should obtain the sponsor's approval for the revision before the IRB/IEC review.

The principal investigator will revise the ICF for his/her site whenever important new information becomes available that may affect patient consent. The principal investigator will obtain the sponsor's approval for the revised ICF, and then the revised ICF must be approved in writing by the IRB/IEC prior to use.

10.2 Informed consent

When a patient is a minor on the day of informed consent, consent should be obtained from the patient's legally acceptable representative (guardian) in addition to the consent from the patient.

1) The investigator has to provide the patient and guardian (as needed) with full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study after the contract is concluded between the principal investigator or the study site, and the sponsor. Patients and guardian (as needed) must be informed that participation is voluntary and that they can withdraw from the study at any time and must be provided with the opportunity to ask questions and allowed time to consider the information provided.
2) The patient's and guardian's (as needed) signed and dated ICF must be obtained before conducting any procedures specific to the study.
3) The investigator has to store the original, signed ICF and provide a copy to the

patient and guardian (as needed).

4) The investigator has to inform the patient and guardian (as needed) in a timely manner if important new information becomes available that may affect the patient's willingness to continue participation in the study. The communication of this information should be documented.

11. Ethical conduct of the study and GCP compliance

11.1 Approval of the study protocol

The final protocol, including the final version of the ICF, must be approved in writing by an IRB/IEC before the initiation of the study. The IRB/IEC must approve any advertisement for patient recruitment, if planned. The study must be re-approved by the IRB/IEC annually, as local regulations require.

11.2 Compliance with the study protocol, GCP and local regulations

The study will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki, with ICH GCP, and with local regulations.

The investigator should conduct the study in an efficient and diligent manner and in accordance with this protocol; generally accepted standards of GCP; and all applicable local regulations relating to the conduct of the clinical study.
The investigator should accept monitoring, audits, IRB/IEC review, and regulatory authority inspection of study-related documents and procedures and provide all study-related source data and documents for direct access.

11.3 Change in the study protocol

All revisions and/or amendments to this protocol should be approved in writing by the sponsor and the appropriate IRB/IEC. The investigator will not make any changes to the conduct of the study or the protocol without first obtaining written approval from the sponsor and the IRB/IEC, except where necessary to eliminate an apparent immediate hazard to a study patient.

If revision of the study protocol is necessary, the revision or new version of the study protocol should be notified to or approved by each IRB/IEC, and if applicable, also the local regulatory authority, before implementation. Local requirements have to be followed.

In the case of administrative changes, the approval of the IRB/IEC is not necessary.

12. Suspension, termination and completion of the study

The sponsor reserves the right to discontinue the study at this site for safety or administrative reason(s) at any time. In particular, a site that does not recruit at an acceptable rate may be discontinued. Should the study be terminated and/or the site closed for whatever reason, the study drug pertaining to the study should be returned to the sponsor or its representative.

If deciding to early terminate or temporarily discontinue the study, the sponsor should notify the investigator and regulatory authorities in writing of the termination or temporary discontinuation with the reasons. The investigator will immediately notify the patients of this decision, give appropriate medical treatment, take necessary measures, and record treatment or measures provided on the source documents.

13. Planned duration of the study

July 2013 to April 2017 (Enrollment: September 2013 to December 2016)

14. Patient privacy protection

The sponsor (or its representative), the IRB/IEC, or the regulatory authority representatives may consult and/or copy study documents in order to verify SAE reports and eCRF data. By signing the ICF, the patient agrees to this process. If study documents are copied during the process of verifying SAE reports and eCRF information, the patient will be identified by subject number only; full names and initials will be masked before transmission to the sponsor. The confidentiality of the patient's personal data shall be protected in accordance with appropriate laws and regulations.

15. Retention of records

The investigator will retain the essential documents specified under the GCP (eg, source document such as medical records, contract, signed consent form) until the latest day shown below. However, this requirement does not always apply to those documents that are not preservable, such as blood samples.

- the day after at least 3 years have elapsed since notification of the discontinuation of clinical development of the study drug by the sponsor if the development is discontinued
- the day after at least 15 years have elapsed since the early study termination or completion of the study
- the day when the period specified by local and/or national requirements have elapsed

The investigator should take measures to prevent accidental or premature destruction of these documents. Documents cannot be destroyed without written sponsor authorization.

16. Payment and compensation

16.1 Payment to the patients

Patients may receive some payment (eg, transportation fee) for participation in the study in accordance with the regulatory requirements.

16.2 Compensation

If patients experience any AEs or injuries due to the study treatment or procedures, the sponsor will compensate them appropriately in accordance with the regulatory requirements.

17. Publication policy

The sponsor intends to use the results of this study for the purposes of national and international registration. If necessary, the authorities will be notified of the investigator's name, address, qualifications, and extent of involvement. Reports covering clinical and biostatistical aspects of the study will be prepared by the sponsor or its representative.

The sponsor encourages publication of clinical research results and, at its sole discretion, may publish results of the study. The investigator and the coordinating investigator may also seek to publish the results of the study. In such instances, prior written approval should be obtained directly from the sponsor. The sponsor reserves the right to review material before presentation or submission to a journal. This ensures consistency with the sponsor's goals.

18. References

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