

Clinical Study Protocol

A Long-Term Study of SM-13496 in Patients with Bipolar I Disorder

Sumitomo Dainippon Pharma Co., Ltd.

Study No.: D1002002
Version: 1.04
Date: March 15, 2016

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List of Abbreviations and Definitions of Terms

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

<u>Abbreviations or special terms</u>	<u>Explanation</u>
ADR	Adverse drug reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass 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
DB baseline	Double-blind baseline, which means the baseline in the prior study (D1002001)
DIEPSS	Drug-Induced Extrapyrmidal 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

<u>Abbreviations or special terms</u>	<u>Explanation</u>
LDL	Low density lipoprotein
LOCF	Last observation carried forward
LT baseline	Long-term baseline, which means the baseline in the present study
MADRS	Montgomery-Åsberg Depression Rating Scale
MAO	Monoamine oxidase
MedDRA	Medical Dictionary for Regulatory Activities
MINI	Mini International Neuropsychiatric Interview
NGSP	National glycohemoglobin standardization program
QOL	Quality of life
QTc	QT interval corrected
QTcB	QTc Bazett
QTcF	QTc Fridericia
SAE	Serious adverse event
SDS	Sheehan Disability Scale
SSRI	Selective serotonin reuptake inhibitor
TEAE	Treatment-emergent adverse event
YMRS	Young Mania Rating Scale
VPA	Valproate/divalproex
WHO	World Health Organization

Protocol Synopsis

Study Title

A Long-Term Study of SM-13496 in Patients with Bipolar I Disorder

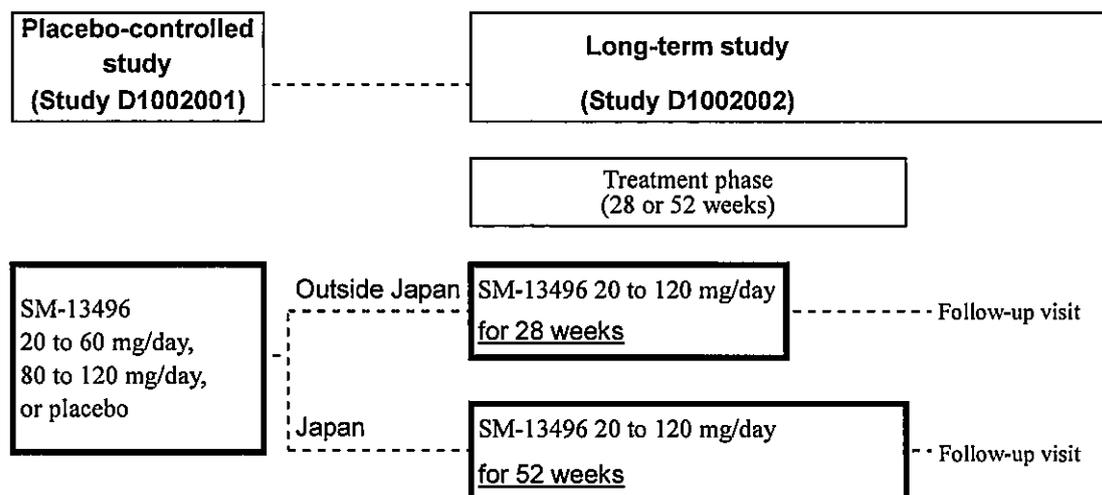
Objectives

The study objective is to evaluate the long-term efficacy and safety of SM-13496 (20-120 mg/day) in patients with bipolar I disorder.

Study design

The study will be conducted in a multi-center and open-label manner.

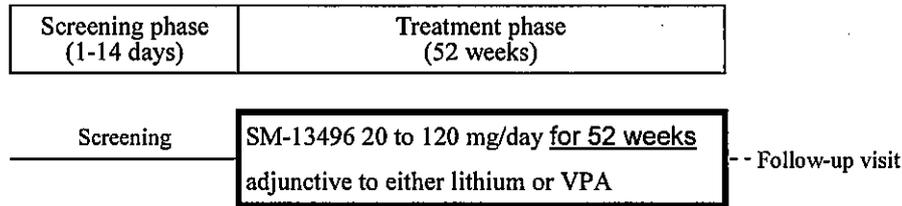
Study flowchart for completers of the placebo-controlled study



Assessments at Week 6 in the placebo-controlled study will be used for baseline in the long-term study.

All patients will visit the study site for a follow-up 14 days (\pm 7 days) after completion or discontinuation.

Study flowchart for patients who did not participate in the placebo-controlled study (in Japan only)



VPA; valproate/divalproex

All patients will visit the study site for a follow-up 14 days (\pm 7 days) after completion or discontinuation.

Subjects

Patients with bipolar I disorder

Inclusion criteria

(1) Patients who completed the prior study:

- 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) Patients who completed the prior study and who are considered by the investigator to be eligible and without safety concerns.
- 3) Patients who agree to use appropriate contraception (see Section 5.5, Page 50) to prevent pregnancy in female patients or the female partners of patients, when the patients or their partners are of childbearing potential.

(2) Patients who did not participate in the prior study:

- 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) Patients aged 18 through 74 years at the time of consent.
- 3) Patients with bipolar I disorder, most recent episode manic, hypomanic, or mixed, with or without rapid cycling disease course (\geq 4 episodes of mood disturbance, but $<$ 8 episodes in the previous 12 months prior to screening) (diagnosed by

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, mixed or depressive episode (preferably with confirmation by a reliable informant such as a family member or caregiver).
- 5) Patients with a negative pregnancy test at screening, when the patients are female and of childbearing potential.
- 6) Patients who agree to use appropriate contraception (see Section 5.5, Page 50) to prevent pregnancy in female patients or the female partners of patients, when the patients or their partners are of childbearing potential.
- 7) Patients who are willing to initiate treatment with either lithium or valproate/divalproex (VPA) during the treatment phase if they are not currently being treated with lithium or VPA at screening. Patient who are willing to continue treatment with either lithium or VPA throughout the study if they are currently being treated with lithium or VPA at screening.
- 8) 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.

Exclusion criteria

(1) Patients who completed the prior study:

- 1) Patients with a score ≥ 4 on the Montgomery-Åsberg Depression Rating Scale (MADRS) item 10 (suicidal thoughts) at Week 6 in the prior study
- 2) 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 a specific plan) or item 5 (active suicidal ideation with specific plan and intent) at Week 6 in the prior study
- 3) Patients with imminent risk of suicide or injury to self, others, or property.
- 4) Patients who are otherwise considered ineligible for the study by the investigator.

(2) Patients who did not participate in the prior study:

- 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 primary focus of

- treatment within 3 months prior to screening.
- 2) Patients have a score ≥ 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 a 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 hospitalized involuntarily
 - 6) Patients with a history of non-response to an adequate trial of 3 or more of the following: antidepressants, antipsychotics, lithium or VPA during the current episode.
 - 7) Patients who received monoamine oxidase (MAO) inhibitor within 21 days prior to screening.
 - 8) Patients who received fluoxetine or a combination of olanzapine and fluoxetine within 28 days prior to screening.
 - 9) Patients who received any depot antipsychotics (sustained-release formulation) within 90 days prior to screening.
 - 10) Patients who received clozapine within 120 days prior to screening.
 - 11) Patients who received electroconvulsive therapy within 90 days prior to screening.
 - 12) Patients with a history of HIV seropositivity.
 - 13) 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.
 - 14) Patients with a history of hypersensitivity (eg, drug-induced anaphylaxis, rash, urticaria, or other allergic reactions) to more than one distinct chemical class of drugs.
 - 15) Patients with previous or existing clinically significant complications, such as serious nervous system, endocrine system (including type I diabetes mellitus), hepatic, renal, hematological, respiratory, cardiovascular (including unstable angina, congestive heart failure), gastrointestinal, urological, or other diseases. Patients who have a history of any such diseases and who are considered ineligible for the study by the investigator.
 - 16) Patients with acute hepatitis, severe chronic hepatitis or marked hepatic dysfunction.

- 17) Patients with a gastrointestinal disease or a surgical history that may affect drug absorption, distribution, metabolism or excretion.
- 18) Patients with any chronic organic disease of the central nervous system (ie, tumor, inflammation, convulsive seizure, vascular disorder, Parkinson's disease, Alzheimer's disease or other types of dementia, myasthenia gravis, or other degenerative diseases).
- 19) Patients with any mental retardation or persistent neurological findings due to serious head injury.
- 20) Patients with a body mass index (BMI) of $\leq 18 \text{ kg/m}^2$ or $\geq 40 \text{ kg/m}^2$ at screening.
- 21) Patients with previous or existing macular or retinal pigment changes.
- 22) 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).
- 23) Patients with a history of neuroleptic malignant syndrome.
- 24) Patients with severe tardive dyskinesia, severe dystonia, or other severe motor dysfunction.
- 25) Patients with an HbA1c (NGSP) value of 8.4% or higher at screening.
- 26) Patients with a history or presence of clinically significant electrocardiography (ECG) abnormality.
- 27) Patients who have received the study medication (including placebo) in a previous clinical study of SM-13496.
- 28) Patients who are breastfeeding.
- 29) 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.
- 30) Patients who are otherwise considered ineligible for the study by the investigator.

Study drug

White film-coated tablets containing 20 mg of lurasidone HCl

Dosage and treatment duration

The study drug administration will be initiated on the day of the baseline visit. SM-13496 will be administered at a flexible dose within the range of 20 to 120 mg orally once daily within 30 minutes after evening meal. The dose of SM-13496 can be increased or decreased by 20 mg/day at the scheduled visits, and can be increased by 20 mg/day at unscheduled visits at least 7 days after the prior visit. Dose increases

will only be permitted once a week between each scheduled visit. When any safety concerns are raised, the dose can be reduced by 20 mg/day at unscheduled visits without waiting for 7 days.

For patients who completed the prior study, SM-13496 will be administered at a dose of 60 mg/day (starting on Day 1) for the first week, and at a flexible dose within a range of 20 to 120 mg/day (starting on Day 8) for 27 weeks (outside Japan) or 51 weeks (in Japan only).

For patients who did not participate in the prior study (in Japan only), SM-13496 will be administered at a dose of 20 mg/day (starting on Day 1) for the first week, and at a flexible dose within a range of 20 to 120 mg/day (starting on Day 8) for 51 weeks. Either lithium or VPA will be administered adjunctively. The dose of lithium and VPA can be modified within the approved range in each participating country based on patient condition and serum concentrations that will be obtained at each study visit. The guidance (see Section 5.3.2.1 (1), Page 47) should be followed on the dose of lithium and VPA and on switching between lithium and VPA.

Concomitant medications and therapies

	Screening Phase	Treatment Phase	Follow-up visit
CYP3A4 inhibitors and inducers	A	A	C
Clozapine	A	A	C
Fluoxetine, olanzapine and fluoxetine combination	A	A	C
Depot antipsychotics	A	A	C
Psychotropics (except for mood stabilizers, antiparkinson drugs, anxiolytics, and hypnotics)	B	A	C
MAO inhibitors	A	A	C
Other investigational drugs and post-marketing clinical study medication	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
Mood stabilizers	B	B	C
Medications for extrapyramidal symptoms	B	B	C
Anxiolytics	B	B	C
Hypnotics	B	B	C
Medications for complications	B	B	C

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

Investigation, measurements, assessments, and study schedule

(1) For patients who completed the prior study, outside Japan:

	Baseline		Treatment phase										Follow-up visit
	1 ^{a)}	2	3 ^{b)}	4 ^{b)}	5 ^{b)}	6 ^{b)}	7 ^{b)}	8 ^{b)}	9 ^{b)}	10 ^{c)}	Dis-continuation ^{e)}		
Study Visit No	1 ^{a)}	2	3 ^{b)}	4 ^{b)}	5 ^{b)}	6 ^{b)}	7 ^{b)}	8 ^{b)}	9 ^{b)}	10 ^{c)}	Dis-continuation ^{e)}	-	
Study timeline (Week)	Day 1	1	2	4	8	12	16	20	24	28	-	-	
Visit window (Day) ^{d)}	1	5 to 9	12 to 16	24 to 32	48 to 64	76 to 92	104 to 120	132 to 148	160 to 176	188 to 204	-	- ^{e)}	
Obtain informed consent ^{d)}	X												
Inclusion/exclusion criteria	X												
IWRS	X	X	X	X	X	X	X	X	X	X ^{b)}	X ^{b)}		
Dispense study drug	X	X	X	X	X	X	X	X	X	X	X		
Treatment compliance		X	X	X	X	X	X	X	X	X	X		
YMRS ^{b)}	X ^{a)}	X	X	X	X	X	X	X	X	X	X		
MADRS ^{b)}	X ^{a)}	X	X	X	X	X	X	X	X	X	X		
CGI-BP-S ^{b)}	X ^{a)}	X	X	X	X	X	X	X	X	X	X		
SDS	X ^{a)}												
HAM-A	X ^{a)}												
C-SSRS	X ^{a)}	X	X	X	X	X	X	X	X	X	X		
DIEFSS	X ^{a)}	X	X	X	X	X	X	X	X	X	X		
Body weight	X ^{a)}	X	X	X	X	X	X	X	X	X	X		
Body temperature, blood pressure, pulse rate	X ^{a)}	X	X	X	X	X	X	X	X	X	X		
12-lead ECG	X ^{a)}												
Laboratory measures ^{b)}	X ^{a)}												
Urine pregnancy test (female) ^{b)}	X ^{a)}												
Serum pregnancy test (female) ^{b)}	X ^{a)}												
Li/VPA serum concentration measurement ^{b)}	X	X	X	X	X	X	X	X	X	X	X		

Study Visit No	Treatment phase											Follow-up visit	
	Baseline	2	3 ^{b)}	4 ^{b)}	5 ^{b)}	6 ^{b)}	7 ^{b)}	8 ^{b)}	9 ^{b)}	10 ^{c)}	Dis-continuation ^{e)}		
1 ^{a)}													
Day 1	Day 1	1	2	4	8	12	16	20	24	28	-	-	-
Visit window (Day) ^{d)}	1	5 to 9	12 to 16	24 to 32	48 to 64	76 to 92	104 to 120	132 to 148	160 to 176	188 to 204	-	-	- ^{e)}
Physical examination/adverse event monitoring	X ^{a)}	X	X	X	X	X	X	X	X	X	X	X	X

- a) Assessments at Week 6 in the prior study will be used for the baseline in the present study.
b) Adverse events will be checked by telephone call every interim week between scheduled visits starting at Visit 3 (Week 2) and after.
c) At Visit 10 (Week 28) or at discontinuation, all assessments and tests will be performed within 72 hours after the final administration of the study drug.
d) Day 1 is defined as the day of the initial administration of the study drug in the treatment phase.
e) All patients will visit the study site for a follow-up 14 days (± 7 days) after Visit 10 (Week 28) or after discontinuation.
f) Written informed consent should be obtained from the patient at Week 6 in the prior study.
g) The patient's final status will be marked in the IWRS at Visit 10 or at discontinuation.
h) When the YMRS or MADRS total score is ≥ 18 or at least one of the CGI-BP-S (overall, depression, mania) scores is ≥ 4 after bipolar disorder symptoms are stabilized (see Section 6.2.7), the YMRS, MADRS and CGI-BP-S should be reassessed at an unscheduled visit within 10 days.
i) Blood will be collected in fasting condition (fasting for at least 10 hours before blood sampling on the day of the scheduled visit).
j) To be performed only in female patients of childbearing potential before menopause.
k) To be performed only in the case of positive urine pregnancy test.
l) To be performed only in patients receiving lithium or VPA.

(2) For patients who completed the prior study, Japan:

	Baseline		Treatment phase													Follow-up visit		
	1 ^{a)}	2	3 ^{b)}	4 ^{b)}	5 ^{b)}	6 ^{b)}	7 ^{b)}	8 ^{b)}	9 ^{b)}	10 ^{b)}	11 ^{b)}	12 ^{b)}	13 ^{b)}	14 ^{b)}	15 ^{b)}		16 ^{c)}	Dis-continuation ^{c)}
Study Visit No	1 ^{a)}	2	3 ^{b)}	4 ^{b)}	5 ^{b)}	6 ^{b)}	7 ^{b)}	8 ^{b)}	9 ^{b)}	10 ^{b)}	11 ^{b)}	12 ^{b)}	13 ^{b)}	14 ^{b)}	15 ^{b)}	16 ^{c)}	Dis-continuation ^{c)}	-
Study timeline (Week)	Day 1	1	2	4	8	12	16	20	24	28	32	36	40	44	48	52	-	-
Visit window (Day) ^{d)}	1	5 to 9	12 to 16	24 to 32	48 to 64	76 to 92	104 to 120	132 to 148	160 to 176	188 to 204	216 to 232	244 to 260	272 to 288	300 to 316	328 to 344	356 to 372	-	- ^{e)}
Obtain informed consent ^{f)}	X																	
Inclusion/exclusion criteria	X																	
IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Treatment compliance	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
YMRS ^{b)}	X ^{a)}	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MADRS ^{b)}	X ^{a)}	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CGI-BP-S ^{b)}	X ^{a)}	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SDS	X ^{a)}	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HAM-A	X ^{a)}	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS	X ^{a)}	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DIEPSS	X ^{a)}	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight	X ^{a)}	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body temperature, blood pressure, pulse rate	X ^{a)}	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X ^{a)}	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory measures ^{b)}	X ^{a)}	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test (female) ^{b)}	X ^{a)}	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Visit No	Treatment phase															Follow-up visit		
	Baseline	2	3 ^{b)}	4 ^{b)}	5 ^{b)}	6 ^{b)}	7 ^{b)}	8 ^{b)}	9 ^{b)}	10 ^{b)}	11 ^{b)}	12 ^{b)}	13 ^{b)}	14 ^{b)}	15 ^{b)}		16 ^{c)}	Dis-continuation ^{e)}
Study timeline (Week)	1 ^{a)}	2	2	4	8	12	16	20	24	28	32	36	40	44	48	52	-	-
Visit window (Day) ^{d)}	1	5 to 9	12 to 16	24 to 32	48 to 64	76 to 92	104 to 120	132 to 148	160 to 176	188 to 204	216 to 232	244 to 260	272 to 288	300 to 316	328 to 344	356 to 372	-	- ^{e)}
Serum pregnancy test (female) ^{k)}	X ^{a)}			X	X	X		X		X		X		X		X		X
Li/VPA serum concentration measurement ^{h)}		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination/adverse event monitoring	X ^{a)}	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

- a) Assessments at Week 6 in the prior study will be used for the baseline in the present study.
- b) Adverse events will be checked by telephone call every interim week between scheduled visits starting at Visit 3 (Week 2) and after.
- c) At Visit 16 (Week 52) or at discontinuation, all assessments and tests will be performed within 72 hours after the final administration of the study drug.
- d) Day 1 is defined as the day of the initial administration of the study drug in the treatment phase.
- e) All patients will visit the study site for a follow-up 14 days (± 7 days) after Visit 16 (Week 52) or after discontinuation.
- f) Written informed consent should be obtained from the patient at Week 6 in the prior study.
- g) The patient's final status will be marked in the IWRS at Visit 16 or at discontinuation.
- h) When the YMRS or MADRS total score is ≥ 18 or at least one of the CGI-BP-S (overall, depression, mania) scores is ≥ 4 after bipolar disorder symptoms are stabilized (see Section 6.2.7), the YMRS, MADRS and CGI-BP-S should be reassessed at an unscheduled visit within 10 days.
- i) Blood will be collected in fasting condition (fasting for at least 10 hours before blood sampling on the day of the scheduled visit).
- j) To be performed only in female patients of childbearing potential before menopause.
- k) To be performed only in the case of positive urine pregnancy test.
- l) To be performed only in patients receiving lithium or VPA.

	Screening phase	Base-line	Treatment phase																Follow-up visit
			1	2	3 ^{b)}	4 ^{b)}	5 ^{b)}	6 ^{b)}	7 ^{b)}	8 ^{b)}	9 ^{b)}	10 ^{b)}	11 ^{b)}	12 ^{b)}	13 ^{b)}	14 ^{b)}	15 ^{b)}	16 ^{c)}	
Study Visit No	0 ^{a)}	1	2	3 ^{b)}	4 ^{b)}	5 ^{b)}	6 ^{b)}	7 ^{b)}	8 ^{b)}	9 ^{b)}	10 ^{b)}	11 ^{b)}	12 ^{b)}	13 ^{b)}	14 ^{b)}	15 ^{b)}	16 ^{c)}	Discontinuation ^{e)}	-
Study timeline (Week)	-	Day 1	1	2	4	8	12	16	20	24	28	32	36	40	44	48	52	-	-
Visit window (Day) ^{d)}	-14 to -1	1	5 to 9	12 to 16	24 to 32	48 to 64	76 to 92	104 to 120	132 to 148	160 to 176	188 to 204	216 to 232	244 to 260	272 to 288	300 to 316	328 to 344	356 to 372	-	- ^{e)}
Laboratory measures ^{f)}	X	X		X	X	X	X		X		X		X		X		X	X	
Hepatitis screening	X								X		X		X		X		X	X	
Urine pregnancy test (female) ^{g)}	X			X	X	X	X		X		X		X		X		X	X	
Serum pregnancy test (female) ^{h)}	X			X	X	X	X		X		X		X		X		X	X	
Li/VPA serum concentration measurement ⁱ⁾	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination/adverse event monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

- a) To be performed after obtaining informed consent, and evaluate patient eligibility within 14 days after initiation of screening.
- b) Adverse events will be checked by telephone call every interim week between scheduled visits at Visit 3 (Week 2) or after.
- c) At Visit 16 (Week 52) or at discontinuation, all assessments and tests will be performed within 72 hours after the final administration of the study drug.
- d) Day 1 is defined as the day of the initial administration of the study drug in the treatment phase.
- e) All patients will visit the study site for a follow-up 14 days (\pm 7 days) after Visit 16 (Week 52) or after discontinuation.
- f) Informed consent can be obtained at Visit 0, but must be done prior to interventional study procedures.
- g) The patient's final status will be marked in the IWRS at Visit 16 or at discontinuation.
- h) When the YMRS or MADRS total score is \geq 18 or at least one of the CGI-BP-S (overall, depression, mania) scores is \geq 4 after bipolar disorder symptoms are stabilized (see Section 6.2.7), the YMRS, MADRS and CGI-BP-S should be reassessed at an unscheduled visit within 10 days.
- i) Blood will be collected in fasting condition (fasting for at least 10 hours before blood sampling on the day of the scheduled visit).
- j) To be performed only in female patients of childbearing potential before menopause.
- k) To be performed only in the case of positive urine pregnancy test.
- l) To be performed only in patients receiving lithium or VPA.

Variables

(1) Efficacy variables

- 1) Change from baseline in the prior study (D1002001) and the present study (D1002002) in the MADRS total score at the final assessment and each assessment point
- 2) Change from baseline in the prior study and the present study in the Young Mania Rating Scale (YMRS) total score at the final assessment and each assessment point
- 3) Change from baseline in the prior study and the present study in the Clinical Global Impressions: Bipolar Version - Severity of Illness (CGI-BP-S) (overall, depression, mania) scores at the final assessment and each assessment point
- 4) Change from baseline in the prior study and the present study in the Sheehan Disability Scale (SDS) score at the final assessment and each assessment point
- 5) Change from baseline in the prior study and the present study in the Hamilton Rating Scale for Anxiety (HAM-A) total score at the final assessment and each assessment point
- 6) The time to recurrence/relapse of any mood event from clinical stability of bipolar disorder. Clinical stability is defined as total scores of ≤ 12 on the MADRS and the YMRS over at least 12 weeks, with the allowance of 2 excursions (the YMRS and/or MADRS total scores up to 13 or 14, respectively) except during the last 4 weeks before achieving clinical stability.
Recurrence/relapse of a mood event is defined as any of the following criteria:
 - a) Fulfilled DSM-IV-TR criteria for major depressive, manic, hypomanic, or mixed episode
 - b) Required treatment intervention for depressive, manic, hypomanic or mixed symptoms with antipsychotics (other than the study drug), antidepressants, mood stabilizers (other than lithium and VPA), anxiolytics or benzodiazepines. Treatment with lorazepam, temazepam, zolpidem, zolpidem CR, eszopiclone, or zaleplon within the permitted dose range (see Section 5.3.2.1, Page 47) is not applied to this criterion.
 - c) Psychiatric hospitalization for any bipolar mood episode
 - d) The YMRS or MADRS total score ≥ 18 or at least one of the CGI-BP-S (overall, depression, mania) scores ≥ 4 at 2 consecutive visits no more than 10 days apart
 - e) Discontinuation from the study because of a mood episode (as determined by the investigator).

(2) 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 prior study (D1002001) and the present study (D1002002) in the Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS) total score (except for the overall severity score) at the final assessment and at each assessment point
- Change from baseline in the prior study and the present study in the individual DIEPSS symptoms scores at the final assessment and at each assessment
- Change from baseline in the prior study and the present study in the serum prolactin concentration at the final assessment and at each assessment point
- Change from baseline in the prior study and the present study in the ECG parameter (QTc) at the final measurement
- Change from baseline in the prior study and the present study in the fasting blood glucose, HbA1c (NGSP), glycoalbumin, total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides at the final measurement
- Change from baseline in the prior study and the present study in the body weight at the final measurement
- Laboratory measures and vital signs
- Proportion of patients with any instance of suicide attempt or suicidal ideation based on the C-SSRS

Target number of patients

- Patients who completed the prior study: 325 patients
- Patients who did not participate in the prior study: 80 patients (Japan only)

Planned duration of the study

July 2013 to April 2018 (Enrollment: September 2013 to February 2017)

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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.

Although it is extremely important to control the acute manifestations of the illness as rapidly and effectively as possible, the true key issue is successful maintenance treatments, ie, the prevention of new episodes and all kinds of complications and disablement. Approximately 90% of patients with bipolar disorder will experience a recurrence within a period of 5 years ⁸⁾, and it has been reported that the time to recurrence will become shorter when recurrences are repeated ⁹⁾. Given these aspects of bipolar disorder, maintenance treatment for prevention of recurrence is also important in addition to the treatment of acute phase depressive symptoms and manic symptoms.

For depressive symptoms associated with bipolar disorder, the guideline ¹⁰⁾ 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 ¹¹⁾ by the Japanese Society of Mood Disorders 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 D₂ and serotonin 5-HT_{2A} receptors, which relate to antipsychotic effects, and 5-HT₇ receptor, which may relate to antidepressant effect and cognitive function ¹²⁾, and the 5-HT_{1A} receptor, which may relate to anxiolytic effect and cognitive function ¹²⁾. 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 disorder have been completed. In the PREVAIL 1 and 2 studies, the reduction in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score (the primary variable) was significantly greater for SM-13496 than for placebo. On the basis of these data, the monotherapy and adjunctive therapy with lithium or valproate for depressive symptoms associated with bipolar I disorder was approved in the United States in 2013 and under regulatory authority's review in Canada. Furthermore, a clinical study (the PERSIST study) is ongoing to evaluate the efficacy of SM-13496 maintenance therapy (prevention of recurrence or relapse of a

bipolar mood episode).

On the basis of the above-mentioned background, the clinical development to investigate SM-13496 for depressive symptoms associated with bipolar disorder and for prevention of recurrence/relapse of mood episodes has been initiated in Japan as well. A placebo-controlled study (Study D1002001) has been planned to evaluate the efficacy and safety of SM-13496 in the patients with current major depressive episodes associated with bipolar I disorder. The study has been also planned to evaluate the long-term efficacy and safety of SM-13496 in patients with bipolar I disorder. The target population will be the completers of Study D1002001 and Japanese patients whose most recent or current episode is mania, hypomania, or mixed. SM-13496 will be administered for 28 or 52 (in Japan only) weeks at a flexibly dose within a range of 20 to 120 mg/day.

2. Objectives

The study objective is to evaluate the long-term efficacy and safety of SM-13496 (20-120 mg/day) in patients with bipolar I disorder.

3. Study design and flowchart

3.1 Study design

The study will be conducted in a multi-center and open-label manner.

3.2 Study method and flowchart

3.2.1 Flowchart and study schedule

The study flowchart is shown in Figure 1 and Figure 2. The completers of the prior study (the placebo-controlled study; D1002001), whose most recent or current episode is depression, and Japanese patients whose most recent or current episode is mania, hypomania, or mixed can be enrolled in the present study.

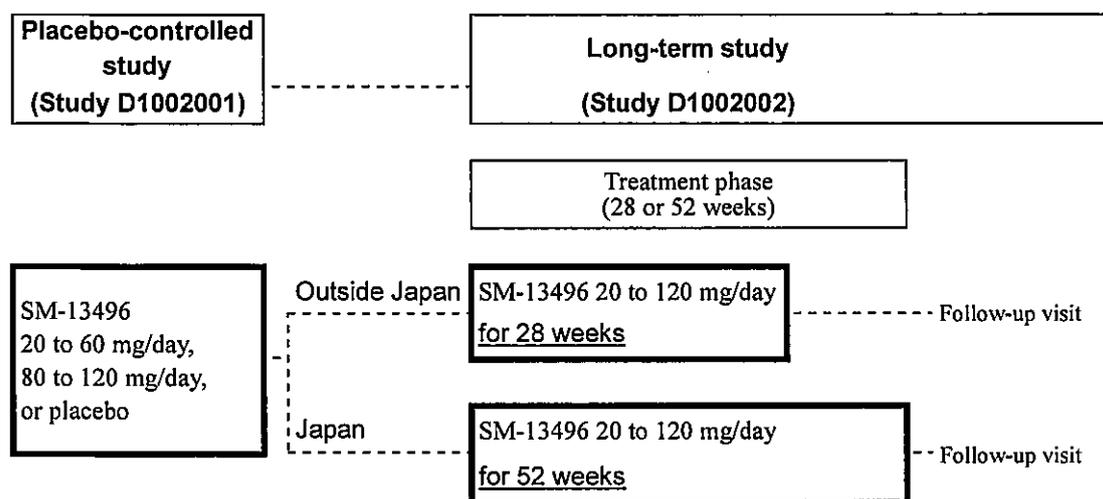
(1) Completers of the prior study

For the patients who completed the prior study, the assessments at Week 6 in the prior study will be used for the baseline in the present study. SM-13496 will be administered at a flexible dose (20-120 mg/day) for 28 weeks (outside Japan) or 52 weeks (Japan).

(2) Patient who did not participate in the prior study

For Japanese patients, whose most recent or current episode is mania, hypomania or mixed, the study consists of the screening phase and the treatment phase. In the treatment phase, SM-13496 will be administered at a flexible dose (20-120 mg/day) with either lithium or valproate/divalproex (VPA) adjunctively for 52 weeks.

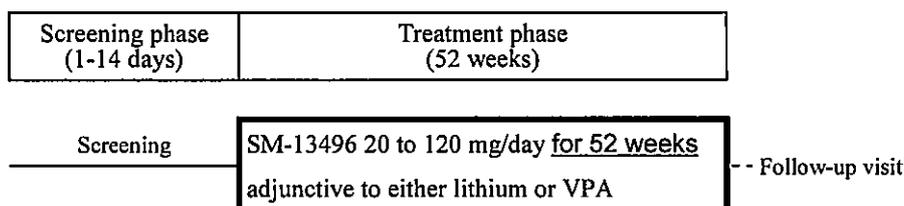
**Figure 1 Study flowchart
(For completers of the placebo-controlled study)**



Assessments at Week 6 in the placebo-controlled study will be used for baseline in the long-term study.

All patients will visit the study site for a follow-up 14 days (\pm 7 days) after completion or discontinuation.

**Figure 2 Study flowchart
(For patients who did not participated in the placebo-controlled study)
(in Japan only)**



VPA; valproate/divalproex

All patients will visit the study site for a follow-up 14 days (\pm 7 days) after completion or discontinuation.

The study schedules are shown in Table 1, Table 2, and Table 3. Day 1 is defined as the day of the initial administration of the study drug in the treatment phase. Day -1 is defined as the day before Day 1 for patients who did not participate in the prior study.

Table 1 Study schedule (patients who completed the prior study, outside Japan)

	Treatment phase											Follow-up visit
	Baseline	2	3 ^{b)}	4 ^{b)}	5 ^{b)}	6 ^{b)}	7 ^{b)}	8 ^{b)}	9 ^{b)}	10 ^{c)}	Dis-continuation ^{e)}	
Study Visit No	1 ^{a)}	2	3 ^{b)}	4 ^{b)}	5 ^{b)}	6 ^{b)}	7 ^{b)}	8 ^{b)}	9 ^{b)}	10 ^{c)}	Dis-continuation ^{e)}	Follow-up visit
Study timeline (Week)	Day 1	1	2	4	8	12	16	20	24	28	-	-
Visit window (Day) ^{d)}	1	5 to 9	12 to 16	24 to 32	48 to 64	76 to 92	104 to 120	132 to 148	160 to 176	188 to 204	-	- ^{e)}
Obtain informed consent ^{f)}	X											
Inclusion/exclusion criteria	X	X	X	X	X	X	X	X	X	X	X ^{g)}	
IWRS	X	X	X	X	X	X	X	X	X	X	X ^{g)}	
Dispense study drug	X	X	X	X	X	X	X	X	X	X	X	
Treatment compliance	X ^{a)}	X	X	X	X	X	X	X	X	X	X	
YMRS ^{b)}	X ^{a)}	X	X	X	X	X	X	X	X	X	X	
MADRS ^{b)}	X ^{a)}	X	X	X	X	X	X	X	X	X	X	
CGI-BP-S ^{b)}	X ^{a)}	X	X	X	X	X	X	X	X	X	X	
SDS	X ^{a)}	X	X	X	X	X	X	X	X	X	X	
HAM-A	X ^{a)}	X	X	X	X	X	X	X	X	X	X	
C-SSRS	X ^{a)}	X	X	X	X	X	X	X	X	X	X	
DIEPSS	X ^{a)}	X	X	X	X	X	X	X	X	X	X	
Body weight	X ^{a)}	X	X	X	X	X	X	X	X	X	X	
Body temperature, blood pressure, pulse rate	X ^{a)}	X	X	X	X	X	X	X	X	X	X	
12-lead ECG	X ^{a)}	X	X	X	X	X	X	X	X	X	X	
Laboratory measures ⁱ⁾	X ^{a)}	X	X	X	X	X	X	X	X	X	X	
Urine pregnancy test (female) ^{j)}	X ^{a)}	X	X	X	X	X	X	X	X	X	X	
Serum pregnancy test (female) ^{k)}	X ^{a)}	X	X	X	X	X	X	X	X	X	X	
Li/VPA serum concentration measurement ^{l)}	X ^{a)}	X	X	X	X	X	X	X	X	X	X	
Physical examination/adverse event monitoring	X ^{a)}	X	X	X	X	X	X	X	X	X	X	X

- a) Assessments at Week 6 in the prior study will be used for the baseline in the present study.
- b) Adverse events will be checked by telephone call every interim week between scheduled visits starting at Visit 3 (Week 2) and after.
- c) At Visit 10 (Week 28) or at discontinuation, all assessments and tests will be performed within 72 hours after the final administration of the study drug.
- d) Day 1 is defined as the day of the initial administration of the study drug in the treatment phase.
- e) All patients will visit the study site for a follow-up 14 days (\pm 7 days) after Visit 10 (Week 28) or after discontinuation.
- f) Written informed consent should be obtained from the patient at Week 6 in the prior study.
- g) The patient's final status will be marked in the IWRS at Visit 10 or at discontinuation.
- h) When the YMRS or MADRS total score is ≥ 18 or at least one of the CGI-BP-S (overall, depression, mania) scores is ≥ 4 after bipolar disorder symptoms are stabilized (see Section 6.2.7), the YMRS, MADRS and CGI-BP-S should be reassessed at an unscheduled visit within 10 days.
- i) Blood will be collected in fasting condition (fasting for at least 10 hours before blood sampling on the day of the scheduled visit).
- j) To be performed only in female patients of childbearing potential before menopause.
- k) To be performed only in the case of positive urine pregnancy test.
- l) To be performed only in patients receiving lithium or VPA.

Table 2 Study schedule (patients who completed the prior study, Japan)

Study Visit No	Treatment phase														Dis- continuation ^{e)}	Follow-up visit	
	Baseline	2	3 ^{b)}	4 ^{b)}	5 ^{b)}	6 ^{b)}	7 ^{b)}	8 ^{b)}	9 ^{b)}	10 ^{b)}	11 ^{b)}	12 ^{b)}	13 ^{b)}	14 ^{b)}			15 ^{b)}
Study Visit No	1 ^{a)}	2	3 ^{b)}	4 ^{b)}	5 ^{b)}	6 ^{b)}	7 ^{b)}	8 ^{b)}	9 ^{b)}	10 ^{b)}	11 ^{b)}	12 ^{b)}	13 ^{b)}	14 ^{b)}	15 ^{b)}	16 ^{c)}	-
Study timeline (Week)	Day 1	1	2	4	8	12	16	20	24	28	32	36	40	44	48	52	-
Visit window (Day) ^{d)}	1	5 to 9	12 to 16	24 to 32	48 to 64	76 to 92	104 to 120	132 to 148	160 to 176	188 to 204	216 to 232	244 to 260	272 to 288	300 to 316	328 to 344	356 to 372	- ^{e)}
Obtain informed consent ^{f)}	X																
Inclusion/exclusion criteria	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Treatment compliance	X ^{a)}	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
YMRS ^{b)}	X ^{a)}	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MADRS ^{b)}	X ^{a)}	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CGI-BP-S ^{b)}	X ^{a)}	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SDS	X ^{a)}	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HAM-A	X ^{a)}	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS	X ^{a)}	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DIEPSS	X ^{a)}	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight	X ^{a)}	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body temperature, blood pressure, pulse rate	X ^{a)}	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X ^{a)}	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory measures ^{b)}	X ^{a)}	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test (female) ^{b)}	X ^{a)}	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Visit No	Treatment phase															Follow-up visit		
	Baseline	2	3 ^{b)}	4 ^{b)}	5 ^{b)}	6 ^{b)}	7 ^{b)}	8 ^{b)}	9 ^{b)}	10 ^{b)}	11 ^{b)}	12 ^{b)}	13 ^{b)}	14 ^{b)}	15 ^{b)}		16 ^{e)}	Dis-continuation ^{e)}
Study timeline (Week)	1 ^{a)}	2																-
Day 1	Day 1	1	2	4	8	12	16	20	24	28	32	36	40	44	48	52	-	-
Visit window (Day) ^{a)}	1	5 to 9	12 to 16	24 to 32	48 to 64	76 to 92	104 to 120	132 to 148	160 to 176	188 to 204	216 to 232	244 to 260	272 to 288	300 to 316	328 to 344	356 to 372	-	- ^{e)}
Serum pregnancy test (female) ^{b)}	X ^{a)}			X		X		X		X		X		X		X		X
Li/VPA serum concentration measurement ^{b)}		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination/adverse event monitoring	X ^{a)}	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

- a) Assessments at Week 6 in the prior study will be used for the baseline in the present study.
- b) Adverse events will be checked by telephone call every interim week between scheduled visits starting at Visit 3 (Week 2) and after.
- c) At Visit 16 (Week 52) or at discontinuation, all assessments and tests will be performed within 72 hours after the final administration of the study drug.
- d) Day 1 is defined as the day of the initial administration of the study drug in the treatment phase.
- e) All patients will visit the study site for a follow-up 14 days (\pm 7 days) after Visit 16 (Week 52) or after discontinuation.
- f) Written informed consent should be obtained from the patient at Week 6 in the prior study.
- g) The patient's final status will be marked in the IWRS at Visit 16 or at discontinuation.
- h) When the YMRS or MADRS total score is ≥ 18 or at least one of the CGI-BP-S (overall, depression, mania) scores is ≥ 4 after bipolar disorder symptoms are stabilized (see Section 6.2.7), the YMRS, MADRS and CGI-BP-S should be reassessed at an unscheduled visit within 10 days.
- i) Blood will be collected in fasting condition (fasting for at least 10 hours before blood sampling on the day of the scheduled visit).
- j) To be performed only in female patients of childbearing potential before menopause.
- k) To be performed only in the case of positive urine pregnancy test.
- l) To be performed only in patients receiving lithium or VPA.

	Screening phase	Base-line	Treatment phase																Follow-up visit
			2	3 ^{b)}	4 ^{b)}	5 ^{b)}	6 ^{b)}	7 ^{b)}	8 ^{b)}	9 ^{b)}	10 ^{b)}	11 ^{b)}	12 ^{b)}	13 ^{b)}	14 ^{b)}	15 ^{b)}	16 ^{c)}	Discontinuation ^{e)}	
Study Visit No	0 ^{a)}	1	2	3 ^{b)}	4 ^{b)}	5 ^{b)}	6 ^{b)}	7 ^{b)}	8 ^{b)}	9 ^{b)}	10 ^{b)}	11 ^{b)}	12 ^{b)}	13 ^{b)}	14 ^{b)}	15 ^{b)}	16 ^{c)}	Discontinuation ^{e)}	-
Study timeline (Week)	-	Day 1	1	2	4	8	12	16	20	24	28	32	36	40	44	48	52	-	-
Visit window (Day) ^{d)}	-14 to -1	1	5 to 9	12 to 16	24 to 32	48 to 64	76 to 92	104 to 120	132 to 148	160 to 176	188 to 204	216 to 232	244 to 260	272 to 288	300 to 316	328 to 344	356 to 372	-	- ^{e)}
Laboratory measures ^{j)}	X	X		X	X		X		X		X		X		X		X	X	
Hepatitis screening	X																		
Urine pregnancy test (female) ^{j)}	X		X	X	X		X		X		X		X		X		X	X	
Serum pregnancy test (female) ^{k)}	X		X	X	X		X		X		X		X		X		X	X	
Li/VPA serum concentration measurement ^{h)}	X	X	X	X	X		X		X		X		X		X		X	X	
Physical examination/adverse event monitoring	X	X	X	X	X		X		X		X		X		X		X	X	X

- a) To be performed after obtaining informed consent, and evaluate patient eligibility within 14 days after initiation of screening.
b) Adverse events will be checked by telephone call every interim week between scheduled visits at Visit 3 (Week 2) or after.
c) At Visit 16 (Week 52) or at discontinuation, all assessments and tests will be performed within 72 hours after the final administration of the study drug.
d) Day 1 is defined as the day of the initial administration of the study drug in the treatment phase.
e) All patients will visit the study site for a follow-up 14 days (\pm 7 days) after Visit 16 (Week 52) or after discontinuation.
f) Informed consent can be obtained at Visit 0, but must be done prior to interventional study procedures.
g) The patient's final status will be marked in the IWRS at Visit 16 or at discontinuation.
h) When the YMRS or MADRS total score is \geq 18 or at least one of the CGI-BP-S (overall, depression, mania) scores is \geq 4 after bipolar disorder symptoms are stabilized (see Section 6.2.7), the YMRS, MADRS and CGI-BP-S should be reassessed at an unscheduled visit within 10 days.
i) Blood will be collected in fasting condition (fasting for at least 10 hours before blood sampling on the day of the scheduled visit).
j) To be performed only in female patients of childbearing potential before menopause.
k) To be performed only in the case of positive urine pregnancy test.
l) To be performed only in patients receiving lithium or VPA.

3.3 Dosage

The study drug administration will be initiated on the day of the baseline visit. SM-13496 will be administered at a flexible dose within a range of 20 to 120 mg orally once daily within 30 minutes after evening meal. The dose of SM-13496 can be increased or decreased by 20 mg/day at the scheduled visits, and can be increased by 20 mg/day at unscheduled visits at least 7 days after the prior visit. Dose increases will only be permitted once a week between each scheduled visit. When any safety concerns are raised, the dose can be reduced by 20 mg/day at unscheduled visits without waiting for 7 days.

For patients who completed the prior study, SM-13496 will be administered at a dose of 60 mg/day (starting on Day 1) for the first week, and at a flexible dose within a range of 20 to 120 mg/day (starting on Day 8) for 27 weeks (outside Japan) or 51 weeks (in Japan only).

For patients who did not participate in the prior study (in Japan only), SM-13496 will be administered at a dose of 20 mg/day (starting on Day 1) for the first week, and at a flexible dose within a range of 20 to 120 mg/day (starting on Day 8) for 51 weeks. Either lithium or VPA will be administered adjunctively. The dose of lithium and VPA can be modified within the approved range in each participating country based on patient condition and serum concentrations that will be obtained at each study visit.

Rationale

The dose of SM-13496 in the present study is same as that in the prior study, 20 to 120 mg/day. Patients who participated in the prior study will have received SM-13496 within a range of 20 to 120 mg/day or placebo in a double-blind manner. For the completers of the prior study, 60 mg/day, which is half the maximum dose in the prior study, was selected for the initial dose in order to avoid an intolerable change in dose of SM-13496.

For patients who did not participate in the prior study, 20 mg/day was selected as the initial dose because a low initial dose followed by a gradual dose escalation is preferable from the safety point of view.

The flexible-dose manner was selected because individual differences in patient condition and symptoms associated with bipolar I disorder vary. Concomitant use of either lithium or VPA will not be mandatory for the completers of the prior study

because these drugs are prohibited in the prior study. On the other hand, for patients who did not participate in the prior study, concomitant use of either lithium or VPA will be mandatory in order to evaluate the long-term efficacy and safety of SM-13496 adjunctive to a mood stabilizer.

3.4 Variables

3.4.1 Efficacy variables

- 1) Change from baseline in the prior study (D1002001) and the present study (D1002002) in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score at the final assessment and each assessment point
- 2) Change from baseline in the prior study and the present study in the Young Mania Rating Scale (YMRS) total score at the final assessment and each assessment point
- 3) Change from baseline in the prior study and the present study in the Clinical Global Impressions: Bipolar Version - Severity of Illness (CGI-BP-S) (overall, depression, mania) scores at the final assessment and each assessment point
- 4) Change from baseline in the prior study and the present study in the Sheehan Disability Scale (SDS) score at the final assessment and each assessment point
- 5) Change from baseline in the prior study and the present study in the Hamilton Rating Scale for Anxiety (HAM-A) total score at the final assessment and each assessment point
- 6) Time to recurrence/relapse of any mood event from clinical stability of bipolar disorder. Clinical stability is defined as total scores of ≤ 12 on the MADRS and the YMRS over at least 12 weeks, with the allowance of 2 excursions (the YMRS and/or MADRS total scores up to 13 or 14, respectively) except during the last 4 weeks before achieving clinical stability. Recurrence/relapse of a mood event is defined as any of the following criteria:
 - a) Fulfilled DSM-IV-TR criteria for major depressive, manic, hypomanic, or mixed episode
 - b) Required treatment intervention for depressive, manic, hypomanic or mixed symptoms with antipsychotics (other than the study drug), antidepressants, mood stabilizers (other than lithium and VPA), anxiolytics or benzodiazepines. Treatment with lorazepam, temazepam, zolpidem, zolpidem CR, eszopiclone, or zaleplon within the permitted dose range (see Section 5.3.2.1, Page 47) is not applied to this criterion.
 - c) Psychiatric hospitalization for any bipolar mood episode

- d) The YMRS or MADRS total score ≥ 18 or at least one of the CGI-BP-S (overall, depression, mania) scores ≥ 4 at 2 consecutive visits no more than 10 days apart
 - e) Discontinuation from the study because of a mood episode (as determined by the investigator).
- 7) Time to all cause discontinuation

Rationale

The MADRS ¹³⁾ 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. The MADRS is a scale that can accurately assess the anti-depressive efficacy of a medication by a uni-dimensional evaluation of psychological symptoms while leaving out physical symptoms and has been used in many clinical studies ^{14), 15)}. The YMRS ¹⁶⁾ is an 11-item scale designed to assess severity of manic symptoms, and frequently used in clinical studies.

The CGI-BP-S ¹⁷⁾ 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, mania, overall) scores were selected for an overall assessment of efficacy against the symptoms associated with bipolar disorder. The SDS ¹⁸⁾ consists of self-rated items designed to assess functional impairments in 3 domains of every daily life (work/school, social life, and communication within the family). The SDS is easy to administer and is not easily influenced by the patient's severity of illness or willingness to use the scale. The HAM-A ¹⁹⁾ 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 ^{14), 15)}.

Preventing recurrence/relapse of mood episodes is important in the treatment of bipolar disorder. The definition of the recurrence/relapse was determined by reference to other clinical studies ^{20), 21)}.

3.4.2 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 prior study (D1002001) and the present study (D1002002) in the Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS) total score (except for the overall severity score) at the final assessment and at each assessment point
- Change from baseline in the prior study and the present study in the individual DIEPSS symptoms scores at the final assessment and at each assessment
- Change from baseline in the prior study and the present study in the serum prolactin concentration at the final assessment and at each assessment point
- Change from baseline in the prior study and the present study in the ECG parameter (QTc) at the final measurement
- Change from baseline in the prior study and the present study in the fasting blood glucose, HbA1c (NGSP), glycoalbumin, total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides at the final measurement
- Change from baseline in the prior study and the present study in the body weight at the final measurement
- Laboratory measures and vital signs
- 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 DIEPSS²²⁾ is an evaluation scale for the extrapyramidal symptoms that are caused by drugs.

Antipsychotics are known to increase serum prolactin concentration²³⁾. Some atypical antipsychotics are known to influence glucose metabolism, lipid metabolism, and body weight. Some drugs affect cardiac rhythm (eg, QT interval prolongation).

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-SSRS²⁴⁾ 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 enrolled patients in the study is as follows:

- Patients who completed the prior study: 325 patients
- Patients who did not participate in the prior study: 80 patients (Japan only)

Rationale

The percentage of patients who completed the PREVAIL 2 study, which has a study design similar to that of the present study, was 74%. Approximately 65% of patients are estimated to enter the present study based on the number of patients who enrolled into the PREVAIL extension study (D1050256) from the PREVAIL 2 study. On the basis of this information, the sample size for the present study was calculated. From considerations of study duration and enrollment speed, approximately 80 Japanese patients will be expected to enroll in the present study.

4. Patient population

The target disease is bipolar I disorder.

4.1 Inclusion criteria

4.1.1 Patients who completed the prior study

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 administration of the study drug.

- 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) Patients who completed the prior study and who are considered by the investigator to be eligible and without safety concerns.
- 3) Patients who agree to use appropriate contraception (see Section 5.5, Page 50) to prevent pregnancy in female patients or the female partners of patients, when the patients or their partners are of childbearing potential.

4.1.2 Patients who did not participate in the prior study

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 administration of the study drug.

- 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) Patients aged 18 through 74 years at the time of consent.
- 3) Patients with bipolar I disorder, most recent episode manic, hypomanic, or mixed, with or without rapid cycling disease course (≥ 4 episodes of mood disturbance, but < 8 episodes in the previous 12 months prior to screening) (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, mixed or depressive episode (preferably with confirmation by a reliable informant such as a family member or caregiver).
- 5) Patients with a negative pregnancy test at screening, when the patients are female and of childbearing potential.
- 6) Patients who agree to use appropriate contraception (see Section 5.5, Page 50) to prevent pregnancy in female patients or the female partners of patients, when the patients or their partners are of childbearing potential.
- 7) Patients who are willing to initiate treatment with either lithium or VPA during the treatment phase if they are not currently being treated with lithium or VPA at screening. Patient who are willing to continue treatment with either lithium or VPA throughout the study if they are currently being treated with lithium or VPA at screening.
- 8) 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.

4.2 Exclusion criteria

4.2.1 Patients who completed the prior study

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

- 1) Patients with a score ≥ 4 on the MADRS item 10 (suicidal thoughts) at Week 6 in the prior study
- 2) Patients with a “Yes” response to the C-SSRS item 4 (active suicidal ideation with some intent to act, without a specific plan) or item 5 (active suicidal ideation with specific plan and intent) at Week 6 in the prior study

- 3) Patients with imminent risk of suicide or injury to self, others, or property.
- 4) Patients who are otherwise considered ineligible for the study by the investigator.

4.2.2 Patients who did not participate in the prior study

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

- 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 primary focus of treatment within 3 months prior to screening.
- 2) Patients have a score ≥ 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 a 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 hospitalized involuntarily
- 6) Patients with a history of non-response to an adequate trial of 3 or more of the following: antidepressants, antipsychotics, lithium or VPA during the current episode.
- 7) Patients who received monoamine oxidase (MAO) inhibitor within 21 days prior to screening.
- 8) Patients who received fluoxetine or a combination of olanzapine and fluoxetine within 28 days prior to screening.
- 9) Patients who received any depot antipsychotics (sustained-release formulation) within 90 days prior to screening.
- 10) Patients who received clozapine within 120 days prior to screening.
- 11) Patients who received electroconvulsive therapy within 90 days prior to screening.
- 12) Patients with a history of HIV seropositivity.
- 13) 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.
- 14) Patients with a history of hypersensitivity (eg, drug-induced anaphylaxis, rash, urticaria, or other allergic reactions) to more than one distinct chemical class of

drugs.

- 15) Patients with previous or existing clinically significant complications, such as serious nervous system, endocrine system (including type I diabetes mellitus), hepatic, renal, hematological, respiratory, cardiovascular (including unstable angina, congestive heart failure), gastrointestinal, urological, or other diseases. Patients who have a history of any such diseases and who are considered ineligible for the study by the investigator.
- 16) Patients with acute hepatitis, severe chronic hepatitis or marked hepatic dysfunction.
- 17) Patients with a gastrointestinal disease or a surgical history that may affect drug absorption, distribution, metabolism or excretion.
- 18) Patients with any chronic organic disease of the central nervous system (ie, tumor, inflammation, convulsive seizure, vascular disorder, Parkinson's disease, Alzheimer's disease or other types of dementia, myasthenia gravis, or other degenerative diseases).
- 19) Patients with any mental retardation or persistent neurological findings due to serious head injury.
- 20) Patients with a body mass index (BMI) of $\leq 18 \text{ kg/m}^2$ or $\geq 40 \text{ kg/m}^2$ at screening.
- 21) Patients with previous or existing macular or retinal pigment changes.
- 22) 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).
- 23) Patients with a history of neuroleptic malignant syndrome.
- 24) Patients with severe tardive dyskinesia, severe dystonia, or other severe motor dysfunction.
- 25) Patients with an HbA1c (NGSP) value of 8.4% or higher at screening.
- 26) Patients with a history or presence of clinically significant ECG abnormality.
- 27) Patients who have received the study medication (including placebo) in a previous clinical study of SM-13496.
- 28) Patients who are breastfeeding.
- 29) 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.
- 30) Patients who are otherwise considered ineligible for the study by the investigator.

4.3 Method of enrolling patients

A unique subject number will be assigned to each patient who provides informed consent by the Interactive Web Response System (IWRS). The subject number consists of [REDACTED]

[REDACTED] If a patient does not meet the study entry criteria, his or her subject number cannot be reassigned to another patient. Patients who did not participate in the prior study (in Japan only) may be re-screened up to 2 times. If a patient is re-screened, he or she will receive a new subject number, which cannot be reassigned to another patient. The subject number will be used for patient identification in all procedures throughout the study.

Before the initiation of the study treatment, the investigator will evaluate patient eligibility and input it into the IWRS.

4.4 Discontinuation of patients from the study

4.4.1 Criteria of discontinuation

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 64) or if any adverse events or lack of efficacy results in psychotic hospitalization.

4.4.2 Procedures for discontinuation

When a patient discontinues before study completion, the investigator should perform all applicable activities scheduled at the time of discontinuation 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 date 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 6.3.1.4 (see Page 58).

4.5 Stay at the study site

For outpatients 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

5.1.1 Identity

SM-13496 20 mg tablets will be used. SM-13496 20 mg tablets are white film-coated tablets containing 20 mg of lurasidone HCl.

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 1 to 6 columns and 9 rows. Each row will contain 1 to 6 tablets of the study drug depending of dose.

5.1.2.2 Labeling

The blister cards of the clinical supplies will 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 sites. 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 drugs 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

The study drug administration will be initiated on the day of the baseline visit. SM-13496 will be administered at a flexible dose within the range of 20 to 120 mg orally once daily within 30 minutes after evening meal. The dose of SM-13496 can be increased or decreased by 20 mg/day at the scheduled visits, and can be increased by 20 mg/day at unscheduled visits at least 7 days after the prior visit. Dose increases will only be permitted once a week between each scheduled visit. When any safety concerns are raised, the dose can be reduced by 20 mg/day at unscheduled visits without waiting for 7 days.

For patients who completed the prior study, SM-13496 will be administered at a dose of 60 mg/day (starting on Day 1) for the first week, and at a flexible dose within a range of 20 to 120 mg/day (starting on Day 8) for 27 weeks (outside Japan) or 51 weeks (in Japan only).

For patients who did not participate in the prior study (in Japan only), SM-13496 will be administered at a dose of 20 mg/day (starting on Day 1) for the first week, and at a flexible dose within a range of 20 to 120 mg/day (starting on Day 8) for 51 weeks. Either lithium or VPA will be administered adjunctively. The dose of lithium and VPA can be modified within the approved range in each participating country based on patient condition and serum concentrations that will be obtaining at each study visit. The guidance should be followed on the dose of lithium and VPA and on switching between lithium and VPA (Section 5.3.2.1 (1), Page 47).

The number of tablets to be taken at a time is shown in Table 4.

Table 4 Number of tablets to be taken once

Daily dose	Number of tablets to be taken at a time
20 mg/day	1 tablet
40 mg/day	2 tablets
60 mg/day	3 tablets
80 mg/day	4 tablets
100 mg/day	5 tablets
120 mg/day	6 tablets

5.2.2 Dispensing study drug

The investigator or a designated person will access the IWRS for dispensing the study drug to patients at Visit 1 (Day 1, baseline) and Visits 2 to 9 (outside Japan) or Visits 2 to 15 (in Japan). 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 1 for the first treatment week, even if the interval between Visit 1 and Visit 2 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 1 to 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 and should not be considered replacements for

lost/damaged study drug. 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 2 to 10 (outside Japan) or Visits 2 to 16 (in Japan) 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 0 and follow-up visit 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 5 shows the restriction on concomitant medications/therapies.

Table 5 Restriction on concomitant medications/therapies

	Screening Phase	Treatment Phase	Follow-up visit
CYP3A4 inhibitors and inducers	A	A	C
Clozapine	A	A	C
Fluoxetine, olanzapine and fluoxetine combination	A	A	C
Depot antipsychotics	A	A	C
Psychotropics (except for mood stabilizers, antiparkinson drugs, anxiolytics, and hypnotics)	B	A	C
MAO inhibitors	A	A	C
Other investigational drugs and post-marketing clinical study medication	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
Mood stabilizers	B	B	C
Medications for extrapyramidal symptoms	B	B	C
Anxiolytics	B	B	C
Hypnotics	B	B	C
Medications for complications	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 0 until the end of the treatment phase.

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

5.3.2 Restricted concomitant medications/therapies

5.3.2.1 Psychotropic medications

(1) Psychotropics (except for mood stabilizers, antiparkinson drugs, anxiolytics, and hypnotics)

Psychotropics excluding mood stabilizers, antiparkinson drugs, anxiolytics, and hypnotics (see Items (2) to (5) in this section) will be restricted as follows:

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

(2) Mood stabilizers

For patients who completed the prior study

Mood stabilizers (excluding lithium and VPA) will be prohibited from the initiation of the study treatment until the end of the study treatment. Either lithium or VPA can be used.

For patients who did not participate in the prior study

Mood stabilizers (excluding lithium and VPA) will be prohibited from the initiation of the study treatment until the end of the study treatment. Either lithium or VPA will be administered adjunctively from the initiation of the study treatment until the end of the study treatment.

Guidance on the dose of lithium and VPA

The dose of lithium and VPA will be in principle within the range approved in each participating country. The dose of lithium and VPA can be modified based on patient condition and serum concentrations that will be obtained at each study visit. If necessary, the investigator can use either lithium or VPA at a lower or higher dose than approved with prior consultation with the medical monitor. If any safety concerns are raised, treatment with either lithium or VPA should be terminated.

Guidance on switching between lithium and VPA

Switching between lithium and VPA will be not recommended, but may be permitted on a case-by-case basis following a consultation with the medical monitor.

(3) Medication for extrapyramidal symptoms (eg, antiparkinson drugs)

Medications for extrapyramidal symptoms (eg, antiparkinson drugs) will be restricted as follows from screening to the end of the study treatment:

- For patients who completed the prior study and who received antiparkinson drugs or other drugs for extrapyramidal symptoms at the initiation of the study treatment, the drugs will be continued without any dosage modification.
- For patients who did not participate in the prior study and who did not receive antiparkinson drugs or other drugs for the treatment of extrapyramidal symptoms at screening, drugs for extrapyramidal symptoms will be prohibited from screening until the initiation of the study treatment.
- For patients who did not participate in the prior study and who received antiparkinson drugs or other drugs for the treatment of 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 6 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 6. For akathisia, propranolol (≤ 120 mg/day), amantadine (≤ 300 mg/day), or one of the drugs listed in Table 6 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 6 Permitted concomitant antiparkinson drugs

<u>Drug</u>	<u>Daily total dose</u>
Biperiden	≤ 16 mg
Trihexyphenidyl	≤ 10 mg
Benztropine	≤ 6 mg
Diphenhydramine	≤ 300 mg

(4) Anxiolytics

From the initiation of the study treatment to the end of the study treatment, only lorazepam (≤ 2 mg/day) can be used as needed for treatment of anxiety, agitation, irritation, and otherwise, but administration will be prohibited within 8 hours before assessment of the MADRS, CGI-BP-S, SDS, HAM-A, YMRS 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. If lorazepam is not effective, another anxiolytics may be used with prior authorization of the medical monitor.

(5) Hypnotics

From the initiation of the study treatment to the end of the study treatment, one of the drugs listed in Table 7 may be used at bedtime for the treatment of insomnia. Hypnotics can be used only once per night, but administration will be prohibited within 8 hours before assessment of the MADRS, CGI-BP-S, SDS, HAM-A, YMRS, and C-SSRS. If the drugs listed in Table 7 are not available at the study site, similar drugs at equivalent doses may be used with prior authorization of the medical monitor. If the selected hypnotic is not effective, another hypnotics not listed in Table 7 may be used with prior authorization of the medical monitor.

Table 7 Permitted hypnotic medication

<u>Drug</u>	<u>Daily total dose</u>
Temazepam	≤ 30 mg
Zolpidem	≤ 10 mg
Zolpidem CR	≤ 12.5 mg
Eszopiclone	≤ 3 mg
Zaleplon	≤ 20 mg

5.3.2.2 Medications for complications

Medication for complications used at the initiation of the study treatment will be continued without any modification of the dosage unless the complications worsen or improve.

5.4 Restrictions for patients

At Visits 1, 4, 6, 8, 10, 12, 14 and 16, and at discontinuation, patients should be fasting for at least 10 hours before blood sampling on the day of the scheduled visit.

5.5 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 the 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, 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, ie, 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 64).

6. Measurements

Study schedule is shown in Table 1, Table 2 and Table 3 (see Pages 27 to 32). The following data will be collected. For completers of the prior study, assessments at Week 6 in the prior study will be used for baseline in the present study, which means any procedures (eg, assessments, measurements, sampling) will not be performed at Visit 1 actually.

6.1 Screening and demographic measurements

The following data will be recorded at screening for patients who did not participate in

the prior study:

- 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 most recent or current episode
 - time of onset of the most recent or current 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 the most recent hospital discharge if hospitalized because of manic, mixed manic or major depressive episodes
 - number of hospitalizations 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) 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). The MINI will be utilized to identify other exclusionary psychiatric diagnoses.
- 6) 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 ¹³⁾ 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) ²⁵⁾ will be used for the MADRS assessment.

A qualified rater at the site will assess the MADRS at all scheduled visits (including at

screening) and at discontinuation. The assessment at Visit 10 (outside Japan) or 16 (in Japan) 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 psychotropic drugs. When the YMRS or MADRS total score is ≥ 18 or at least one of the CGI-BP-S (overall, depression, mania) scores is ≥ 4 after bipolar disorder symptoms are stabilized (see Section 6.2.7), the MADRS should be reassessed at an unscheduled visit within 10 days.

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 in the prior or present study.

6.2.2 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 16 and at discontinuation. The assessment at Visit 10 (outside Japan) or 16 (in Japan) 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 psychotropic drugs. When the YMRS or MADRS total score is ≥ 18 or at least one of the CGI-BP-S (overall, depression, mania) scores is ≥ 4 after bipolar disorder symptoms are stabilized (see Section 6.2.7), the YMRS should be reassessed at an unscheduled visit within 10 days.

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 in the prior or present study.

6.2.3 Clinical Global Impressions: Bipolar Version – Severity of Illness (CGI-BP-S)

The CGI-BP-S¹⁷⁾ 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 16 and at discontinuation. The assessment at Visit 10 (outside Japan) or 16 (in Japan) 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 psychotropic drugs. When the YMRS or MADRS total score is ≥ 18 or at least one of the CGI-BP-S (overall, depression, mania) scores is ≥ 4 after bipolar disorder symptoms are stabilized (see Section 6.2.7), the CGI-BP-S should be reassessed at an unscheduled visit within 10 days.

6.2.4 Sheehan Disability Scale (SDS)

The SDS¹⁸⁾ 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. The patient will rate 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.

At Visits 1, 4, 6, 8, 10, 12, 14 and 16 and at discontinuation, the patients will rate the disability. The assessment at Visit 10 (outside Japan) or 16 (in Japan) 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 psychotropic drugs.

6.2.5 Hamilton Rating Scale for Anxiety (HAM-A)

The HAM-A¹⁹⁾ 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 1, 4, 6, 8, 10, 12, 14 and 16 and at discontinuation. The assessment at Visit 10 (outside Japan) or 16 (in Japan) 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 psychotropic drugs.

6.2.6 Clinical stability of bipolar disorder

Clinical stability of bipolar disorder is defined as total scores of ≤ 12 on the MADRS and YMRS over at least 12 weeks, with the allowance of 2 excursions (the YMRS and/or MADRS total scores up to 13 or 14, respectively) except during the last 4 weeks before achieving clinical stability. For example, when the YMRS total score is 13 and the MADRS total score is 14 on the same day, this is defined as one excursion. The date when achieving clinical stability will be recorded in the eCRFs.

6.2.7 Recurrence or relapse of mood event

The date of recurrence or relapse of a mood event, the criterion that was met, and the type of recurring or relapsing event (major depressive, manic, hypomanic, or mixed) will be recorded in the eCRFs. Recurrence/relapse of a mood event is defined as any of the following criteria:

- a) Fulfilled DSM-IV-TR criteria for major depressive, manic, hypomanic, or mixed episode
- b) Required treatment intervention for depressive, manic, hypomanic or mixed symptoms with antipsychotics (other than the study drug), antidepressants, mood stabilizers (other than lithium and VPA), anxiolytics or benzodiazepines. However, treatment with lorazepam, temazepam, zolpidem, zolpidem CR, eszopiclone, or zaleplon within the permitted dose range (see Section 5.3.2.1, Page 47) is not applied to this criterion.
- c) Psychiatric hospitalization for any bipolar mood episode
- d) The YMRS or MADRS total score ≥ 18 or at least one of the CGI-BP-S (overall, depression, mania) scores ≥ 4 at 2 consecutive visits no more than 10 days apart
- e) Discontinuation from the study because of a mood event (as determined by the investigator)

When the YMRS or MADRS total score is ≥ 18 or at least one of the CGI-BP-S (overall, depression, mania) scores is ≥ 4 after bipolar disorder symptoms are stabilized, the YMRS, MADRS and CGI-BP-S should be reassessed at an unscheduled visit within 10 days.

The number of mood episodes in the treatment phase will be recorded in the eCRFs for each episode type (major depressive, manic, hypomanic, or mixed).

6.3 Safety measurements

6.3.1 Adverse events

6.3.1.1 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

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 6.3.1.3, Page 57); 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 patient/event outcome or action criteria usually associated with events that pose a threat to a patient'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.

6.3.1.2 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.

6.3.1.3 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.

6.3.1.4 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.

6.3.2 Laboratory tests

Blood and urine samples for the laboratory tests will be collected at Visits 0 (only for Japanese patients who did not participate in the prior study), 1, 4, 6, 8, 10, 12, 14 and 16 and at discontinuation, and will be submitted to the central laboratory for analysis. At Visit 10 (outside Japan) or 16 (in Japan) 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. All 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 8.

Table 8 Contents of the laboratory variables

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

a) Fasting condition will not be mandatory at screening for patients who did not participate in the prior study.

b) Hepatitis tests will be performed only at screening for patients who did not participate in the prior study.

A pregnancy test (urine chorionic gonadotropin) will be performed in female patients of childbearing potential before menopause at the study site at Visits 0 (only for Japanese patients who did not participate in the prior study) or 1 (for completers of the prior study), Visits 4, 6, 8, 10, 12, 14 and 16, 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.

6.3.3 Vital signs

Body temperature, pulse rate, systolic and diastolic blood pressure (sitting), and body weight will be measured at all scheduled visits (including at screening) and at discontinuation. The measurements at Visit 10 (outside Japan) or 16 (in Japan), and at discontinuation should be performed within 72 hours after the final administration of the study drug and before the post treatment with antipsychotics.

6.3.4 12-lead Electrocardiography (ECG)

At Visits 0 (only for Japanese patients who did not participate in the prior study), 1, 4, 6, 8, 10, 12, 14 and 16 and at discontinuation, a 12-lead ECG will be performed on the patients at rest. The test at Visit 10 (outside Japan) or 16 (in Japan), and at discontinuation should be performed within 72 hours after the final administration of the study drug and before the 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.

6.3.5 Drug-Induced Extrapyramidal Symptom Scale (DIEPSS)

The DIEPSS²²⁾ 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 1 to 16 and at discontinuation. The assessment at Visit 10 (outside Japan) or 16 (in Japan) or at discontinuation should be performed within 72 hours after the final administration of the study drug and before the post treatment with antipsychotics.

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

The C-SSRS²⁴⁾ 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 all scheduled visits (including at screening) and at discontinuation. The ‘baseline/screening’ version will be used at screening for patients who did not participate in the prior study. The ‘since last visit’ version will be used at the other visits and at discontinuation for all patients. The assessment at Visit 10 (outside Japan) or 16 (in Japan) or at discontinuation should be performed within 72 hours after the final administration of the study drug and before the post treatment with antipsychotics. The rater should receive specific training before his or her initial assessment of the C-SSRS in the prior or present study.

6.3.7 Blood concentration of lithium or valproate

From patients receiving lithium or VPA, the amount of blood specified in Table 9 or 10 will be collected to obtain 0.5 mL of serum at all scheduled visits (including at screening) and at discontinuation during the period when a patient is receiving either lithium or VPA. Blood concentration of lithium or valproate will be measured at the central laboratory.

6.3.8 Total volume of blood sampling

The total volume of blood to be drawn from each patient is shown in Table 9 and Table 10.

Table 9 Volume of blood sampling from each patient (outside Japan)

	Sample volume (mL)	No. of samples	Total volume (mL)
Hematology	2	4	8
Blood chemistry, TSH, FT4, Li/VPA concentration	11.5 3.5 ^{a)}	4 5 ^{a)}	46 17.5 ^{a)}
Total and free testosterone (male only)	10	4	40
Total			111.5 (male) 71.5 (female)

a) Only in patients receiving Li/VPA.

Table 10 Volume of blood sampling from each patient (in Japan)

For patients who completed the prior study			For patients who did not participate in the prior study		
Sample volume (mL)	No. of samples	Total volume (mL)	Sample volume (mL)	No. of samples	Total volume (mL)

Hematology	2	7	14	2	9	18
Blood chemistry, TSH, FT4, hepatitis, Li/VPA concentration	11.5	7	80.5	13	1	13
	3.5 ^{a)}	8 ^{a)}	28 ^{a)}	11.5	8	92
				3.5 ^{a)}	8 ^{a)}	28 ^{a)}
Total and free testosterone (male only)	10	7	70	10	9	90
Total			192.5 (male)			241 (male)
			122.5 (female)			151 (female)

a) Only in patients receiving Li/VPA.

6.4 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) MINI
- 2) MADRS
- 3) C-SSRS
- 4) HAM-A
- 5) YMRS
- 6) SDS
- 7) DIEPSS
- 8) 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, D1002002)
- 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) Dose of the study drug
- 10) Start date of SAE
- 11) Causality assessment (if sufficient information is available to make this classification)
- 12) History of any ADRs
- 13) Relevant special conditions of the patient
- 14) History of the current disease and treatment for the disease
- 15) Details of the SAE
- 16) Treatment for the SAE
- 17) Details of study treatments
- 18) Details of concomitant medications
- 19) Details on course of the SAE
- 20) 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 (11) 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, D1002002)
- 2) Subject number
- 3) Person who is pregnant (ie, study patient or partner of a 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) Dose of the study drug
- 8) Date pregnancy confirmed by HCG assay
- 9) 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.

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, D1002002)
- 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) Dose of the study drug
- 8) Details of overdose
- 9) 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 62).

8. Quality management

8.1 Monitoring

The study will be monitored at all stages of its development by the 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 eCRF with the patient's medical records (original documents, data, and records). The investigator will be required to store all source documents.

For this 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
- The date when achieving clinical stability
- The date of recurrence or relapse of a mood event and the criterion
- 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 such as 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 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 the 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 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. After source data verification, all the data will be validated by the sponsor or its representative. Missing or inconsistent data will be clarified with the investigator using the EDC system.

After confirming the entered data, the principal investigator will electronically sign the eCRFs to verify the accuracy of the 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/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 data cut after the completion of evaluation for all patients at 28 weeks for the purpose of the regulatory submission. If any changes are made to the statistical analysis proposed below after the study initiation, the changes to the plan will be listed with the reason in the statistical analysis plan.

9.2 Analysis population

All efficacy and safety analyses will be performed on the safety population. The safety population will consist of all patients who take at least one dose of the study drug.

9.3 Handling of data

9.3.1 Treatment groups

Summary tables will be presented for all patients and also be provided by following the 5 groups based on the treatment group in the prior study, whenever appropriate:

- 1) Patients in the 20-60 mg group in the prior study (D1002001)
- 2) Patients in the 80-120 mg group in the prior study
- 3) Patients in either the 20-60 mg group or the 80-120 mg group in the prior study
- 4) Patients in the placebo group in the prior study
- 5) Patients who did not participate in the prior study (ie, no treatment assignment in the prior study)

9.3.2 Day 1

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

9.3.3 Analysis visits, baseline, and post-baseline

All data will be organized and analyzed according to the scheduled timing outlined in Table 1, Table 2 and Table 3 (see Page 27 to 32) and according to the visits denoted on the eCRF. Unscheduled visits will not be used for analyses unless otherwise specified. For patients who completed the prior study, the double-blind baseline (DB baseline) will be defined as the baseline of the prior study, and the long-term baseline (LT baseline) will be defined as Week 6 in the prior study. For patients who did not participate in the prior study, the LT baseline will be defined as the last non-missing data on or before Day 1. Post-baseline data will be defined as the non-missing data on or after Day 1 and through 7 days after the date of final administration of the study drug. The data collected at discontinuation visit will be mapped to the next scheduled visit of the actual discontinuation date.

9.3.4 Summary statistics

Continuous variables will be summarized using descriptive statistics of the number of patients, mean, median, standard deviation or standard error, minimum and maximum values. Categorical variables will be reported as frequencies and percentages. Standard laboratory shift tables will be reported.

9.3.5 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. The method of handling of missing data will

be a last observation carried forward (LOCF) method, and the LOCF method will be applied to 28 weeks visit for all patients and 52 weeks visit for patients enrolled in Japan. The final post LT baseline value up to 28 weeks will be defined as the Week 28 LOCF endpoint record for all patients. Similarly, the final post LT baseline value will be carried forward and will be defined as the Week 52 LOCF endpoint record.

9.4 Demographics and other baseline characteristics

Demographics, baseline characteristics, prior medications, concomitant medications, and exposure to the study drug will be summarized for all patients and by treatment group in the prior study.

9.5 Efficacy analysis

9.5.1 Hypothesis

The study has no hypothesis because of the nature of an open-labeled single-arm study.

9.5.2 Efficacy analysis

Summary statistics in the following efficacy variables will be provided for all patients and by treatment group in the prior study. Note that summaries at visits after 28 weeks as well as at Week 52 (LOCF) will only be provided for patients enrolled in Japan.

- Change from DB and LT baselines in the MADRS total score at each scheduled assessment, Week 28 (LOCF) and Week 52 (LOCF)
- Change from DB and LT baselines in the YMRS total score at each scheduled assessment, Week 28 (LOCF) and Week 52 (LOCF)
- Change from DB and LT baselines in the CGI-BP-S score (overall, depression, mania) at each scheduled assessment, Week 28 (LOCF) and Week 52 (LOCF)
- Change from DB and LT baselines in the SDS total score at each scheduled assessment, Week 28 (LOCF) and Week 52 (LOCF)
- Change from DB and LT baselines in the HAM-A total score at each scheduled assessment, Week 28 (LOCF) and Week 52 (LOCF)

For the following variables, median survival time, its 95% confidence interval using the product-limit method will be calculated and Kaplan-Meier curve will be plotted for all patients and by treatment group in the prior study. The numbers and percentages of patients who experience a recurrence/relapse and all cause discontinuation will be summarized.

- Time to recurrence/relapse from the time when the symptoms associated with

- bipolar disorder have stabilized (see Section 3.4.1, Page 34)
- Time to all cause discontinuation from Day 1

Time to recurrence/relapse will also be analyzed separately for each type of episode of recurrence/relapse (major depressive, manic, hypomanic, or mixed episode) in the same way.

9.5.3 Subgroup analysis

Subgroup analysis will be conducted for the change from DB and LT baselines in efficacy variables, such as the MADRS total score, the YMRS total score, the CGI-BP-S score (overall, depression, mania) and the HAM-A total score, as well as for the time to recurrence/relapse and time to all cause discontinuation, whenever appropriate. Subgroups will include country, sex, age, mood stabilizer (lithium, VPA, or none), most recent or current episode (major depressive, manic, hypomanic, or mixed episode), bipolar I diagnosis subtype (rapid cycling or non-rapid cycling) and psychotic features (with or without). Selected subgroup analyses will be repeated for patients enrolled in Japan. Details of subgroup analysis will be provided in the statistical analysis plan.

9.6 Safety analysis

9.6.1 Adverse events

The number and percentage of patients with at least one AE or ADR for each preferred term and system organ class will be summarized for all patients and by treatment group in the prior study. This summary will be repeated for deaths, SAEs, AEs leading to study discontinuation, AEs by severity, extrapyramidal AEs, and AEs by occurrence timing. 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 summary of AEs will be limited to treatment-emergent AEs (TEAEs), and two kinds of TEAEs will be defined as follows:

- TEAEs (up to 28 weeks): AEs with onset on or after Day 1 through 28 weeks
- TEAEs (up to 52 weeks): AEs with onset on or after Day 1 through 52 weeks

9.6.2 DIEPSS

Summary statistics for observed values and changes from DB and LT baseline in the DIEPSS total score (excluding overall severity) and the individual DIEPSS scores will be provided at each visit, Week 28 (LOCF) and Week 52 (LOCF) for all patients and

by treatment group in the prior study. Note that summaries at visits after 28 weeks as well as at Week 52 (LOCF) will only be provided for patients enrolled in Japan.

9.6.3 C-SSRS

The number and percentage of patients with suicidality will be summarized for all patients and by treatment group in the prior study, 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 for all patients and by treatment group in the prior study. These summaries will be provided by each visit and for overall (up to 28 weeks and up to 52 weeks, respectively).

9.6.4 Concomitant medications

Numbers and percentages of patients with concomitant use of antiparkinson drugs, mood stabilizers, hypnotics, and anxiolytics will be summarized for all patients and by treatment group in the prior study. These summaries will be provided for overall (up to 28 weeks and up to 52 weeks, respectively).

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

Summary statistics for observed values and changes from DB and LT baseline in laboratory tests, vital signs, body weights, and 12-lead ECG parameters will be provided for each visit, Week 28 (LOCF) and Week 52 (LOCF) for all patients and by treatment group in the prior study. Categorical variables will be summarized by presenting shift-tables. Note that summaries at visits after 28 weeks as well as at Week 52 (LOCF) will only be provided for patients enrolled in Japan.

The incidence of markedly abnormal post-baseline laboratory values (MAPLV), markedly abnormal post-baseline vital signs (MAPVS), and prolonged QTc will be summarized for the all patients and by treatment group in the prior study. In these analyses, post-baseline data obtained at unscheduled visits will be taken into consideration. These summaries will be provided for overall (up to 28 weeks and up to 52 weeks, respectively).

9.6.6 Subgroup analysis

Subgroup analysis will be conducted in AE summaries and changes from DB and LT baselines in the DIEPSS total score, serum prolactin concentration, fasting blood glucose, HbA1c (NGSP), glycoalbumin, total cholesterol, LDL cholesterol, HDL

cholesterol, triglycerides, body weight, and ECG parameter (QTc). Subgroups will include country, sex, age and mood stabilizer, most recent or current episode. Selected subgroup analyses will be repeated for patients enrolled in Japan. Details of subgroup analysis will be provided in the statistical analysis plan.

9.7 Interim Analysis

No formal interim analysis is planned.

9.8 Multiplicity considerations

The study has no hypotheses.

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 prior to 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 prior to 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 to 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 2018 (Enrollment: September 2013 to February 2017)

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, and 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 will encourage 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 must be obtained directly from the sponsor. The sponsor reserves

the right to review material prior to presentation or submission to a journal. This ensures consistency with the sponsor's goals.

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