Clinical trial results:
A Long-Term Study of SM-13496 in Patients with Bipolar I Disorder.

Summary

EudraCT number	2013-003039-31
Trial protocol	LT SK
Global end of trial date	17 February 2018

Results information

Result version number	v1 (current)
This version publication date	03 May 2019
First version publication date	03 May 2019

Trial information

Trial identification

Sponsor protocol code	D1002002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01986114
WHO universal trial number (UTN)	-
Other trial identifiers	JapicCTI: 132319

Notes:

Sponsors

Sponsor organisation name	Sumitomo Dainippon Pharma Co. Ltd.
Sponsor organisation address	1-13-1 Kyobashi, Chuo-ku, Tokyo, Japan, 104-8356
Public contact	Drug Development Division, Sumitomo Dainippon Pharmaceutical, cc@ds-pharma.co.jp
Scientific contact	Drug Development Division, Sumitomo Dainippon Pharmaceutical, cc@ds-pharma.co.jp

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 April 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 February 2018
Global end of trial reached?	Yes
Global end of trial date	17 February 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The study evaluates the long-term efficacy and safety of SM-13496 in patients with bipolar I disorder.

Protection of trial subjects:

This study was conducted in accordance with the protocol, ICH GCP, local regulations, and the ethical principles that had their origin in the Declaration of Helsinki. The study was conducted in accordance with applicable local law(s) and regulation(s).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 January 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Japan: 199
Country: Number of subjects enrolled	Malaysia: 11
Country: Number of subjects enrolled	Philippines: 8
Country: Number of subjects enrolled	Russian Federation: 129
Country: Number of subjects enrolled	Taiwan: 7
Country: Number of subjects enrolled	Ukraine: 117
Country: Number of subjects enrolled	Lithuania: 9
Country: Number of subjects enrolled	Slovakia: 15
Worldwide total number of subjects	495
EEA total number of subjects	24

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0

Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	474
From 65 to 84 years	21
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The completers of the prior study (the placebo-controlled study; D1002001) whose most recent or current episode was depression, and newly recruited Japanese subjects whose most recent or current episode was mania, hypomania, or mixed could be enrolled in the present study.

Pre-assignment

Screening details:

For newly recruited Japanese subjects, the study consisted of the screening phase (1-14 days) and the treatment phase. SM-13496 was administered at a flexible dose (20-120 mg/day) for 28 weeks (outside Japan) or 52 weeks (in Japan).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	SM-13496 20-120mg

Arm description:

once daily orally

SM-13496 (lurasidone HCl): SM-13496 20-120mg

Arm type	Experimental
Investigational medicinal product name	SM-13496
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

SM-13496 20, 40, 60, 80, 100, or 120 mg/day, as 20 mg tablets, were administered orally once daily within 30 minutes after evening meal. For subjects who had completed the prior study, SM-13496 was 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) thereafter. For subjects who had not participated in the prior study, SM-13496 was 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) thereafter.

Number of subjects in period 1	SM-13496 20-120mg
Started	495
Completed	339
Not completed	156
Consent withdrawn by subject	58
Adverse event, non-fatal	59
Other reason	7
Lost to follow-up	5
Lack of efficacy	23

Noncompliance	3
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	SM-13496 20-120mg
Reporting group description: once daily orally SM-13496 (lurasidone HCl): SM-13496 20-120mg	

Reporting group values	SM-13496 20-120mg	Total	
Number of subjects	495	495	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	474	474	
From 65-84 years	21	21	
85 years and over	0	0	
Age Continuous Units: years			
arithmetic mean	42.6		
standard deviation	± 12.78	-	
Gender categorical Units: Subjects			
Female	259	259	
Male	236	236	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	225	225	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	270	270	
More than one race	0	0	
Unknown or Not Reported	0	0	
Region of Enrollment Units: Subjects			
Japan	199	199	
Philippines	8	8	
Taiwan	7	7	
Ukraine	117	117	
Malaysia	11	11	
Slovakia	15	15	

Lithuania	9	9	
Russia	129	129	

Subject analysis sets

Subject analysis set title	SM-13496 20-120mg (Overall, 28 weeks)
Subject analysis set type	Safety analysis

Subject analysis set description:

once daily orally

SM-13496 (lurasidone HCl): SM-13496 20-120mg flexibly dosed up to 28 weeks

Subject analysis set title	SM-13496 20-120mg (Japan, 52 weeks)
Subject analysis set type	Safety analysis

Subject analysis set description:

once daily orally

SM-13496 (lurasidone HCl): SM-13496 20-120mg flexibly dosed up to 52 weeks

Reporting group values	SM-13496 20-120mg (Overall, 28 weeks)	SM-13496 20-120mg (Japan, 52 weeks)	
Number of subjects	495	199	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous Units: years			
arithmetic mean	42.6	41.6	
standard deviation	± 12.78	± 11.97	
Gender categorical Units: Subjects			
Female	259	97	
Male	236	102	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	225	199	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	270	0	
More than one race	0	0	
Unknown or Not Reported	0	0	

Region of Enrollment Units: Subjects			
Japan	199	199	
Philippines	8	0	
Taiwan	7	0	
Ukraine	117	0	
Malaysia	11	0	
Slovakia	15	0	
Lithuania	9	0	
Russia	129	0	

End points

End points reporting groups

Reporting group title	SM-13496 20-120mg

Reporting group description:

once daily orally

SM-13496 (lurasidone HCl): SM-13496 20-120mg

Subject analysis set title	SM-13496 20-120mg (Overall, 28 weeks)
Subject analysis set type	Safety analysis

Subject analysis set description:

once daily orally

SM-13496 (lurasidone HCl): SM-13496 20-120mg flexibly dosed up to 28 weeks

Subject analysis set title	SM-13496 20-120mg (Japan, 52 weeks)
Subject analysis set type	Safety analysis

Subject analysis set description:

once daily orally

SM-13496 (lurasidone HCl): SM-13496 20-120mg flexibly dosed up to 52 weeks

Primary: Incidence of adverse events (AEs) and adverse drug reactions (ADRs)

End point title	Incidence of adverse events (AEs) and adverse drug reactions (ADRs)[1]

End point description:

The number of subjects with at least one adverse events and adverse drug reactions

End point type	Primary

End point timeframe:

28, 52 weeks

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The number of subjects with at least one AE or ADR for each preferred term (PT) and system organ class (SOC) were summarized for all subjects. Detailed results are reported in the Adverse events section.

End point values	SM-13496 20-120mg (Overall, 28 weeks)	SM-13496 20-120mg (Japan, 52 weeks)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	495	199		
Units: subjects	352	169		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from long term study baseline to LOCF Endpoint in the Montgomery-Asberg Depression Rating Scale (MADRS) score

End point title	Change from long term study baseline to LOCF Endpoint in the Montgomery-Asberg Depression Rating Scale (MADRS) score

End point description:

Montgomery-Asberg Depression Rating Scale (MADRS)is a clinician-rated assessment of a subject's level of depression.

The MADRS total score ranges from a minimum of 0 to a maximum of 60. For the MADRS total score, low scores indicate a better outcome and high scores indicate a worse outcome. When change from baseline is considered, a negative (decrease in score) value is considered a better outcome, and a positive (increase in score) value is considered a worse outcome.

The MADRS contains ten (10) items. The total score is computed as the sum of the scores for the 10 items.

End point type	Secondary

End point timeframe:

Baseline, 52 weeks and each month

End point values	SM-13496 20-120mg (Overall, 28 weeks)	SM-13496 20-120mg (Japan, 52 weeks)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	494	198		
Units: units on a scale				
arithmetic mean (standard deviation)	-4.4 (± 12.09)	1.1 (± 12.58)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from long term study baseline to LOCF Endpoint in the Young Mania Rating Scale (YMRS) total score.

End point title	Change from long term study baseline to LOCF Endpoint in the Young Mania Rating Scale (YMRS) total score.

End point description:

YMRS (Young Mania Rating Scale) is a clinician-rated assessment of the severity of mania in subjects with a diagnosis of bipolar disorder.

The YMRS total score ranges from a minimum of 0 to a maximum of 60. For the YMRS total score, low scores indicate a better outcome and high scores indicate a worse outcome. When change from baseline is considered, a negative (decrease in score) value is considered a better outcome, and a positive (increase in score) value is considered a worse outcome.

The YMRS contains eleven (11) items. The total score is computed as the sum of the scores for the 11 items.

End point type	Secondary

End point timeframe:

Baseline, 52 weeks and each month

End point values	SM-13496 20-120mg (Overall, 28 weeks)	SM-13496 20-120mg (Japan, 52 weeks)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	494	198		
Units: units on a scale				
arithmetic mean (standard deviation)	-1.0 (± 4.54)	-2.0 (± 6.73)		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of recurrence/relapse of any mood event from clinical stability of bipolar disorder.

End point title	Rate of recurrence/relapse of any mood event from clinical stability of bipolar disorder.

End point description:

The number of subjects who experienced recurrence/relapse of any mood event from clinical stability of bipolar disorder.

End point type	Secondary

End point timeframe:

Baseline to 52 weeks

End point values	SM-13496 20-120mg (Overall, 28 weeks)	SM-13496 20-120mg (Japan, 52 weeks)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	495	199		
Units: subjects				
With relapse or recurrence	14	18		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event data was collected for 28 weeks (outside Japan) and 52 weeks (Japan).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	SM-13496 20-120mg (Overall, 28 weeks)

Reporting group description:

once daily orally

SM-13496 (lurasidone HCl): SM-13496 20-120mg flexibly dosed up to 28 weeks

Reporting group title	SM-13496 20-120mg (Japan, 52 weeks)

Reporting group description:

once daily orally

SM-13496 (lurasidone HCl): SM-13496 20-120mg flexibly dosed up to 52 weeks

Serious adverse events	SM-13496 20-120mg (Overall, 28 weeks)	SM-13496 20-120mg (Japan, 52 weeks)	
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 495 (3.84%)	12 / 199 (6.03%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Blood potassium decreased			
subjects affected / exposed	1 / 495 (0.20%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glucose urine present			
subjects affected / exposed	1 / 495 (0.20%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	1 / 495 (0.20%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine cancer			
subjects affected / exposed	0 / 495 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Pelvic fracture			
subjects affected / exposed	1 / 495 (0.20%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Akathisia			
subjects affected / exposed	1 / 495 (0.20%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychomotor hyperactivity			
subjects affected / exposed	1 / 495 (0.20%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	8 / 495 (1.62%)	3 / 199 (1.51%)	
occurrences causally related to treatment / all	2 / 8	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Alcoholism			
subjects affected / exposed	1 / 495 (0.20%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination, auditory			
subjects affected / exposed	1 / 495 (0.20%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination, visual			

subjects affected / exposed	1 / 495 (0.20%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mania			
subjects affected / exposed	1 / 495 (0.20%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	1 / 495 (0.20%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	3 / 495 (0.61%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Lumbar spinal stenosis			
subjects affected / exposed	1 / 495 (0.20%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 495 (0.20%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 495 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lactic acidosis			
subjects affected / exposed	0 / 495 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	SM-13496 20-120mg (Overall, 28 weeks)	SM-13496 20-120mg (Japan, 52 weeks)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	250 / 495 (50.51%)	137 / 199 (68.84%)	
Investigations			
Weight increased			
subjects affected / exposed	31 / 495 (6.26%)	17 / 199 (8.54%)	
occurrences (all)	31	17	
Nervous system disorders			
Akathisia			
subjects affected / exposed	91 / 495 (18.38%)	60 / 199 (30.15%)	
occurrences (all)	104	64	
Headache			
subjects affected / exposed	37 / 495 (7.47%)	16 / 199 (8.04%)	
occurrences (all)	46	19	
Parkinsonism			
subjects affected / exposed	34 / 495 (6.87%)	15 / 199 (7.54%)	
occurrences (all)	43	25	
Somnolence			
subjects affected / exposed	41 / 495 (8.28%)	24 / 199 (12.06%)	
occurrences (all)	44	24	
Dystonia			
subjects affected / exposed	13 / 495 (2.63%)	10 / 199 (5.03%)	
occurrences (all)	15	11	
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	16 / 495 (3.23%)	10 / 199 (5.03%)	
occurrences (all)	17	11	
Gastrointestinal disorders			
Nausea			

subjects affected / exposed	35 / 495 (7.07%)	24 / 199 (12.06%)	
occurrences (all)	38	25	
Diarrhoea			
subjects affected / exposed	14 / 495 (2.83%)	10 / 199 (5.03%)	
occurrences (all)	15	11	
Vomiting			
subjects affected / exposed	17 / 495 (3.43%)	13 / 199 (6.53%)	
occurrences (all)	21	13	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	51 / 495 (10.30%)	53 / 199 (26.63%)	
occurrences (all)	63	72	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported