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

Summary

EudraCT number	2013-003038-34
Trial protocol	LT SK
Global end of trial date	16 February 2017

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	D1002001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01986101
WHO universal trial number (UTN)	-
Other trial identifiers	JapicCTI: 132318

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	25 April 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 February 2017
Global end of trial reached?	Yes
Global end of trial date	16 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The study evaluates the efficacy and safety of SM-13496 compared with placebo in patients with Bipolar I Depression.

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	19 February 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: 179
Country: Number of subjects enrolled	Malaysia: 19
Country: Number of subjects enrolled	Philippines: 11
Country: Number of subjects enrolled	Russian Federation: 145
Country: Number of subjects enrolled	Taiwan: 13
Country: Number of subjects enrolled	Ukraine: 132
Country: Number of subjects enrolled	Lithuania: 10
Country: Number of subjects enrolled	Slovakia: 16
Worldwide total number of subjects	525
EEA total number of subjects	26

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)	507
From 65 to 84 years	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects were to be evaluated for eligibility during a Screening period of 3-14 days, during which subjects were to be tapered off all psychotropic medications in a manner consistent with labeling recommendations and conventional medical practice.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

once daily orally

Placebo: Placebo comparator

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo tablets were to be administered orally, once daily within 30 minutes after the evening meal.

Arm title	SM-13496 20 - 60 mg/day

Arm description:

once daily orally

SM-13496: SM-13496 20mg for Days 1-7 and flexibly dosed at 20-60 mg/day for Weeks 2 to 6 (starting on Day 8)

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,or 60 mg/day, as 20 mg tablets, were administered orally once daily within 30 minutes after evening meal. SM-13496 dosing
was to be fixed at 20 mg/day for Days 1 to 7 in the 20-60 mg/day treatment arm. SM-13496 was to be flexibly dosed for Weeks 2 to 6 (starting on Day 8).

Arm title	SM-13496 80 - 120 mg/day

Arm description:

once daily orally

SM-13496: SM-13496 20 mg/day for Days 1-2, 40 mg/day for Days 3-4, 60 mg/day for Days 5-6 and

80 mg/day on Day 7 and flexibly dosed at 80-120 mg/day for Weeks 2 to 6 (starting on Day 8)

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.
Subjects randomized to the SM-13496 80-120 mg/day treatment arm were to receive SM-13496 20 mg/day on Days 1 and 2, 40 mg/day on Days 3 and 4, 60 mg/day on Days 5 and 6, and 80 mg/day on Day 7. SM-13496 was to be flexibly dosed for Weeks 2 to 6 (starting on Day 8).

Number of subjects in period 1	Placebo	SM-13496 20 - 60 mg/day	SM-13496 80 - 120 mg/day
Started	172	184	169
Intent-to-Treat Population	171	182	169
Safety Population	172	184	169
Completed	139	157	137
Not completed	33	27	32
Consent withdrawn by subject	14	13	5
Adverse event, non-fatal	7	6	16
Other reason	3	-	-
Lost to follow-up	1	1	-
Lack of efficacy	8	6	11
Noncompliance	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description: once daily orally Placebo: Placebo comparator	
Reporting group title	SM-13496 20 - 60 mg/day
Reporting group description: once daily orally SM-13496: SM-13496 20mg for Days 1-7 and flexibly dosed at 20-60 mg/day for Weeks 2 to 6 (starting on Day 8)	
Reporting group title	SM-13496 80 - 120 mg/day
Reporting group description: once daily orally SM-13496: SM-13496 20 mg/day for Days 1-2, 40 mg/day for Days 3-4, 60 mg/day for Days 5-6 and 80 mg/day on Day 7 and flexibly dosed at 80-120 mg/day for Weeks 2 to 6 (starting on Day 8)	

Reporting group values	Placebo	SM-13496 20 - 60 mg/day	SM-13496 80 - 120 mg/day
Number of subjects	172	184	169
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	166	177	164
From 65-84 years	6	7	5
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	41.2	42.7	43.2
standard deviation	± 12.63	± 12.84	± 12.78
Gender categorical Units: Subjects			
Female	95	96	88
Male	77	88	81
Race/Ethnicity, Customized Units: Subjects			
White	95	105	103
Asian	77	79	66
Region of Enrollment Units: Subjects			
Japan	60	66	53

Philippines	5	3	3
Taiwan	5	4	4
Ukraine	44	43	45
Malaysia	7	6	6
Slovakia	5	7	4
Lithuania	2	4	4
Russia	44	51	50
Montgomery-Åsberg Depression Rating Scale (MADRS) Total Score			
Units: units on a scale			
arithmetic mean	30.9	30.6	30.8
standard deviation	± 5.37	± 5.55	± 5.09
Clinical Global Impression Bipolar Version, Severity of Illness (CGI-BP-S) Score (Depression)			
Units: units on a scale			
arithmetic mean	4.60	4.58	4.58
standard deviation	± 0.689	± 0.705	± 0.603

Reporting group values	Total		
Number of subjects	525		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	507		
From 65-84 years	18		
85 years and over	0		
Age Continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	279		
Male	246		
Race/Ethnicity, Customized			
Units: Subjects			
White	303		
Asian	222		
Region of Enrollment			
Units: Subjects			
Japan	179		
Philippines	11		
Taiwan	13		
Ukraine	132		
Malaysia	19		

Slovakia	16		
Lithuania	10		
Russia	145		
Montgomery-Åsberg Depression Rating Scale (MADRS) Total Score			
Units: units on a scale			
arithmetic mean			
standard deviation	-		
Clinical Global Impression Bipolar Version, Severity of Illness (CGI-BP-S) Score (Depression)			
Units: units on a scale			
arithmetic mean			
standard deviation	-		

Subject analysis sets

Subject analysis set title	Intention-to-treat population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population consisted of all subjects who were randomized and took at least one dose of the study drug in the treatment phase, regardless of any protocol deviations, and who had baseline and at least one post-baseline evaluable MADRS total score.

Reporting group values	Intention-to-treat population		
Number of subjects	522		
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	42.4		
standard deviation	± 12.77		
Gender categorical			
Units: Subjects			
Female	277		
Male	245		
Race/Ethnicity, Customized			
Units: Subjects			
White	302		
Asian	220		
Region of Enrollment			
Units: Subjects			

Japan	178		
Philippines	11		
Taiwan	12		
Ukraine	131		
Malaysia	19		
Slovakia	16		
Lithuania	10		
Russia	145		
Montgomery-Åsberg Depression Rating Scale (MADRS) Total Score			
Units: units on a scale			
arithmetic mean	30.8		
standard deviation	± 5.35		
Clinical Global Impression Bipolar Version, Severity of Illness (CGI-BP-S) Score (Depression)			
Units: units on a scale			
arithmetic mean	4.58		
standard deviation	± 0.666		

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

once daily orally

Placebo: Placebo comparator

Reporting group title	SM-13496 20 - 60 mg/day

Reporting group description:

once daily orally

SM-13496: SM-13496 20mg for Days 1-7 and flexibly dosed at 20-60 mg/day for Weeks 2 to 6 (starting on Day 8)

Reporting group title	SM-13496 80 - 120 mg/day

Reporting group description:

once daily orally

SM-13496: SM-13496 20 mg/day for Days 1-2, 40 mg/day for Days 3-4, 60 mg/day for Days 5-6 and 80 mg/day on Day 7 and flexibly dosed at 80-120 mg/day for Weeks 2 to 6 (starting on Day 8)

Subject analysis set title	Intention-to-treat population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population consisted of all subjects who were randomized and took at least one dose of the study drug in the treatment phase, regardless of any protocol deviations, and who had baseline and at least one post-baseline evaluable MADRS total score.

Primary: Change from baseline in Montgomery-Asberg Depression Rating Scale (MADRS) total score at Week 6

End point title	Change from baseline in Montgomery-Asberg Depression Rating Scale (MADRS) total score at Week 6

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	Primary

End point timeframe:

Baseline to 6 weeks

End point values	Placebo	SM-13496 20 - 60 mg/day	SM-13496 80 - 120 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	171	182	169	
Units: units on a scale				
least squares mean (standard error)	-10.6 (± 0.72)	-13.6 (± 0.69)	-12.6 (± 0.73)	

Statistical analyses

Statistical analysis title	Contrast (Placebo vs. SM-13496 20-60 mg/day)
Comparison groups	Placebo v SM-13496 20 - 60 mg/day
Number of subjects included in analysis	353
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007 [1]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.9
upper limit	-1
Variability estimate	Standard error of the mean
Dispersion value	1

Notes:

[1] - Hochberg-adjusted

Statistical analysis title	Contrast (Placebo vs. SM-13496 80-120 mg/day)
Comparison groups	Placebo v SM-13496 80 - 120 mg/day
Number of subjects included in analysis	340
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.057 [2]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	1.03

Notes:

[2] - Hochberg-adjusted.

Secondary: Change from baseline in the CGI-BP-S (depression) score at Week 6

End point title	Change from baseline in the CGI-BP-S (depression) score at Week 6

End point description:

Clinical Global Impression Bipolar Version, Severity of Illness (CGI-BP-S) score (depression) is a clinician-rated assessment of a subject's level of depression.

The CGI depression score ranges from a minimum of 1 to a maximum of 7. For the CGI depression 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.

End point type	Secondary

End point timeframe:

Baseline to 6 weeks

End point values	Placebo	SM-13496 20 - 60 mg/day	SM-13496 80 - 120 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	171	182	169	
Units: units on a scale				
least squares mean (standard error)	-1.11 (± 0.092)	-1.51 (± 0.088)	-1.41 (± 0.093)	

Statistical analyses

Statistical analysis title	Contrast (Placebo vs. SM-13496 80-120 mg/day)
Comparison groups	Placebo v SM-13496 80 - 120 mg/day
Number of subjects included in analysis	340
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.019
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.56
upper limit	-0.05
Variability estimate	Standard error of the mean
Dispersion value	0.13

Statistical analysis title	Contrast (Placebo vs. SM-13496 20-60 mg/day)
Comparison groups	Placebo v SM-13496 20 - 60 mg/day

Number of subjects included in analysis	353
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.65
upper limit	-0.15
Variability estimate	Standard error of the mean
Dispersion value	0.127

Secondary: Change from baseline in the SDS total score at Week 6(LOCF)

End point title	Change from baseline in the SDS total score at Week 6(LOCF)

End point description:

Sheehan Disability Scale (SDS) total score is a subject-rated assessment of a subject's level of depression.

The SDS total score ranges from a minimum of 0 to a maximum of 30. For the SDS 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 SDS contains three (3) items. The total score is computed as the sum of the scores for the 3 items.

End point type	Secondary

End point timeframe:

Baseline to 6 weeks

End point values	Placebo	SM-13496 20 - 60 mg/day	SM-13496 80 - 120 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	128	147	124	
Units: units on a scale				
least squares mean (standard error)	-5.7 (± 0.66)	-7.6 (± 0.62)	-6.8 (± 0.67)	

Statistical analyses

Statistical analysis title	Contrast (Placebo vs. SM-13496 20-60 mg/day)
Comparison groups	Placebo v SM-13496 20 - 60 mg/day

Number of subjects included in analysis	275
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.037
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.6
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	0.89

Statistical analysis title	Contrast (Placebo vs. SM-13496 80-120 mg/day)
Comparison groups	Placebo v SM-13496 80 - 120 mg/day
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.223
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.9
upper limit	0.7
Variability estimate	Standard error of the mean
Dispersion value	0.92

Secondary: Change from baseline in the YMRS total score at Week 6(LOCF)

End point title	Change from baseline in the YMRS total score at Week 6(LOCF)

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 to 6 weeks

End point values	Placebo	SM-13496 20 - 60 mg/day	SM-13496 80 - 120 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	171	182	169	
Units: units on a scale				
least squares mean (standard error)	-0.51 (± 0.190)	-0.98 (± 0.180)	-0.99 (± 0.191)	

Statistical analyses

Statistical analysis title	Contrast (Placebo vs. SM-13496 20-60 mg/day)
Comparison groups	Placebo v SM-13496 20 - 60 mg/day
Number of subjects included in analysis	353
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.076
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.98
upper limit	0.05
Variability estimate	Standard error of the mean
Dispersion value	0.262

Statistical analysis title	Contrast (Placebo vs. SM-13496 80-120 mg/day)
Comparison groups	Placebo v SM-13496 80 - 120 mg/day
Number of subjects included in analysis	340
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.075
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.01
upper limit	0.05
Variability estimate	Standard error of the mean
Dispersion value	0.269

Secondary: Change from baseline in the HAM-A total score at Week 6(LOCF)	
End point title	Change from baseline in the HAM-A total score at Week 6(LOCF)

End point description:

The Hamilton Rating Scale for Anxiety (HAM-A) scale is a rating scale developed to quantify the severity of anxiety symptomatology.

The HAM-A total score ranges from a minimum of 0 to a maximum of 56. For the HAM-A 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 HAM-A contains fourteen (14) items. The total score is computed as the sum of the scores for the 14 items.

End point type	Secondary

End point timeframe:

Baseline to 6 weeks

End point values	Placebo	SM-13496 20 - 60 mg/day	SM-13496 80 - 120 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	164	179	167	
Units: units on a scale				
least squares mean (standard error)	-5.7 (± 0.51)	-7.4 (± 0.49)	-6.4 (± 0.50)	

Statistical analyses

Statistical analysis title	Contrast (Placebo vs. SM-13496 20-60 mg/day)
Comparison groups	Placebo v SM-13496 20 - 60 mg/day
Number of subjects included in analysis	343
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.016
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.1
upper limit	-0.3
Variability estimate	Standard error of the mean
Dispersion value	0.7

Statistical analysis title	Contrast (Placebo vs. SM-13496 80-120 mg/day)
Comparison groups	Placebo v SM-13496 80 - 120 mg/day
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.294
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	0.7
Variability estimate	Standard error of the mean
Dispersion value	0.71

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 6 weeks	
Adverse event reporting additional description: Safety population is analyzed.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups	
Reporting group title	Placebo
Reporting group description: once daily orally Placebo	
Reporting group title	SM-13496 20 - 60 mg/day
Reporting group description: once daily orally SM-13496 (lurasidone HCl): SM-13496 20 mg/day for Days 1-7, beginning day 8 flexibly dosed 20-60 mg/day	
Reporting group title	SM-13496 80 - 120 mg/day
Reporting group description: once daily orally SM-13496 (lurasidone HCl): SM-13496 20 mg/day for Days 1-2, 40 mg/day for Days 3-4, 60 mg/day for Days 5-6 and 80 mg/day on Day 7 and 80-120 mg/day	

Serious adverse events	Placebo	SM-13496 20 - 60 mg/day	SM-13496 80 - 120 mg/day
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 172 (2.91%)	2 / 184 (1.09%)	4 / 169 (2.37%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Tendon rupture			
subjects affected / exposed	0 / 172 (0.00%)	0 / 184 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			

subjects affected / exposed	1 / 172 (0.58%)	0 / 184 (0.00%)	0 / 169 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	1 / 172 (0.58%)	0 / 184 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 172 (0.58%)	0 / 184 (0.00%)	0 / 169 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Bipolar I disorder			
subjects affected / exposed	1 / 172 (0.58%)	0 / 184 (0.00%)	0 / 169 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mania			
subjects affected / exposed	1 / 172 (0.58%)	1 / 184 (0.54%)	0 / 169 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Panic attack			
subjects affected / exposed	0 / 172 (0.00%)	0 / 184 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	0 / 172 (0.00%)	1 / 184 (0.54%)	0 / 169 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 172 (0.00%)	0 / 184 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo	SM-13496 20 - 60 mg/day	SM-13496 80 - 120 mg/day
Total subjects affected by non-serious adverse events			
subjects affected / exposed	44 / 172 (25.58%)	49 / 184 (26.63%)	75 / 169 (44.38%)
Nervous system disorders			
Akathisia			
subjects affected / exposed	11 / 172 (6.40%)	24 / 184 (13.04%)	40 / 169 (23.67%)
occurrences (all)	12	27	46
Headache			
subjects affected / exposed	15 / 172 (8.72%)	5 / 184 (2.72%)	9 / 169 (5.33%)
occurrences (all)	22	7	11
Parkinsonism			
subjects affected / exposed	4 / 172 (2.33%)	4 / 184 (2.17%)	10 / 169 (5.92%)
occurrences (all)	7	4	19
Somnolence			
subjects affected / exposed	7 / 172 (4.07%)	7 / 184 (3.80%)	11 / 169 (6.51%)
occurrences (all)	8	7	12
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	10 / 172 (5.81%)	12 / 184 (6.52%)	20 / 169 (11.83%)
occurrences (all)	13	13	23
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	8 / 172 (4.65%)	10 / 184 (5.43%)	6 / 169 (3.55%)
occurrences (all)	8	10	6

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