Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of SEP-4199 for the Treatment of Major Depressive Episode Associated with Bipolar I Disorder (Bipolar I Depression)

Summary

EudraCT number	2018-000103-16
Trial protocol	BG SK PL
Global end of trial date	23 April 2020

Results information

Result version number	v2 (current)
This version publication date	04 June 2023
First version publication date	23 April 2021
Version creation reason	
Summary attachment (see zip file)	null (PharmaCM_ Print Preview-updated.pdf)

Trial information

Trial identification

Sponsor protocol code	SEP380-201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03543410
WHO universal trial number (UTN)	-
Other trial identifiers	Japan: jRCT2031220302

Notes:

Sponsors

Sponsor organisation name	Sunovion Pharmaceuticals Inc.
Sponsor organisation address	84 Waterford Drive, Marlboro, United States, 01752
Public contact	CNS Medical Director, Sunovion Pharmaceuticals Inc., 01 18665036351, ClinicalTrialDisclosure@sunovion.com
Scientific contact	CNS Medical Director, Sunovion Pharmaceuticals Inc., 01 18665036351, ClinicalTrialDisclosure@sunovion.com

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	23 April 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 April 2020
Global end of trial reached?	Yes
Global end of trial date	23 April 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of SEP-4199 200 mg/day and 400 mg/day compared with placebo for major depressive episode associated with bipolar I disorder (diagnosed by DSM-5 criteria) as measured by Montgomery-Asberg Depression Rating Scale (MADRS) total score

Protection of trial subjects:

The study was conducted according to the protocol, ICH Good Clinical Practice (GCP), ICH guidelines, and the ethical principles that have their origin in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 June 2018
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	Bulgaria: 43
Country: Number of subjects enrolled	Japan: 49
Country: Number of subjects enrolled	Poland: 11
Country: Number of subjects enrolled	Russian Federation: 46
Country: Number of subjects enrolled	Serbia: 63
Country: Number of subjects enrolled	Slovakia: 19
Country: Number of subjects enrolled	Ukraine: 67
Country: Number of subjects enrolled	United States: 43
Worldwide total number of subjects	341
EEA total number of subjects	73

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	339
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total 344 subjects were randomized in this study. Three subjects, who were randomized but never received any dose of study medication, were not included in the reporting.

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, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	SEP-4199 200 mg

Arm description:

SEP-4199 200 mg/day (supplied in two 100mg tablets)

Arm type	Experimental
Investigational medicinal product name	SEP-4199
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

200 mg/day (supplied in two 100mg tablets)

Arm title	SEP-4199 400 mg

Arm description:

SEP-4199 400 mg/day (supplied in two 200mg tablets)

Arm type	Experimental
Investigational medicinal product name	SEP-4199
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

400 mg /day (supplied in two tablets)

Arm title	Placebo

Arm description:

Placebo (supplied in two tablets/day)

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:
supplied in two tablets

Number of subjects in period 1	SEP-4199 200 mg	SEP-4199 400 mg	Placebo
Started	113	114	114
Completed	92	101	99
Not completed	21	13	15
Consent withdrawn by subject	5	2	8
NON-COMPLIANCE WITH STUDY DRUG	-	-	2
Adverse event, non-fatal	10	8	2
Not Due to COVID-19	2	-	1
Lost to follow-up	-	1	-
Due to COVID-19	4	-	2
Lack of efficacy	-	1	-
Protocol deviation	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	SEP-4199 200 mg
Reporting group description:	
SEP-4199 200 mg/day (supplied in two 100mg tablets)	
Reporting group title	SEP-4199 400 mg
Reporting group description:	
SEP-4199 400 mg/day (supplied in two 200mg tablets)	
Reporting group title	Placebo
Reporting group description:	
Placebo (supplied in two tablets/day)	

Reporting group values	SEP-4199 200 mg	SEP-4199 400 mg	Placebo
Number of subjects	113	114	114
Age Categorical Units: Participants			
<=18 years	1	1	1
Between 18 and 65 years	112	111	113
>=65 years	0	2	0
Age Continuous Units: Years			
arithmetic mean	42	44.4	43.3
standard deviation	± 11.65	± 12.72	± 12.10
Gender, Male/Female Units: Participants			
Female	69	76	64
Male	44	38	50
Age, Customized Units: Subjects			
18-64 years	113	112	114
>=65 years	0	2	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	1	0
Asian	16	16	17
Black or African American	6	8	8
More than one race	0	0	0
Native Hawaiian or Other Pacific Islander	1	2	1
Unknown or Not Reported	0	0	0
White	89	87	88
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	3	3	2
Not Hispanic or Latino	110	109	112
Unknown or Not Reported	0	2	0
Country Name Units: Subjects			

Bulgaria	11	10	22
Japan	16	16	17
Poland	5	1	5
Russia	18	20	8
Serbia	19	26	18
Slovakia	8	5	6
Ukraine	22	20	25
United States	14	16	13
Region of Enrollment Units: Subjects			
Europe	83	82	84
Japan	16	16	17
United States	14	16	13
Baseline BMI Category Units: Subjects			
< 18.5 kg/m2	0	3	0
18.5 - <25.0 kg/m2	51	50	45
25.0 - <30.0 kg/m2	42	33	40
>=30.0 kg/m2	20	28	29
Baseline Weight (kg) Units: kg			
arithmetic mean	75.3	74.8	77.5
standard deviation	± 14.47	± 16.19	± 16.59
Baseline CGI-BP-S Depression Score			
Measure Description: Clinical Global Impressions - Severity: Bipolar Version (CGI-BP-S) score (depression) is a single value, clinician-rated assessment of illness severity, and 7-point scale with range from 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; 7 = among the most extremely ill subjects. A higher score is associated with greater illness severity.			
Units: units on a scale			
arithmetic mean	4.8	4.8	4.9
standard deviation	± 0.66	± 0.65	± 0.70
Baseline MADRS Total Score			
Measure Description: MADRS is a clinician-rated assessment of the subject's level of depression. The measure contains 10 items that measure apparent and reported sadness, inner tension, reduced sleep and appetite, difficulty concentrating, lassitude, inability to feel, and pessimistic and suicidal thoughts, each ranging from 0 to 6. The MADRS total score ranges from 0 to 60, with higher scores indicating increased depressive symptoms			
Units: units on a scale			
arithmetic mean	33.5	33.8	34.1
standard deviation	± 5.77	± 5.63	± 5.35
Baseline BMI (kg/m^2) Units: kg/m^2			
arithmetic mean	26.2	26.6	27
standard deviation	± 4.53	± 4.91	± 4.94

Reporting group values	Total		
Number of subjects	341		
Age Categorical Units: Participants			
<=18 years	3		
Between 18 and 65 years	336		
>=65 years	2		

Age Continuous Units: Years arithmetic mean standard deviation	- -		
Gender, Male/Female Units: Participants			
Female	209		
Male	132		
Age, Customized Units: Subjects			
18-64 years	339		
>=65 years	2		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	2		
Asian	49		
Black or African American	22		
More than one race	0		
Native Hawaiian or Other Pacific Islander	4		
Unknown or Not Reported	0		
White	264		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	8		
Not Hispanic or Latino	331		
Unknown or Not Reported	2		
Country Name Units: Subjects			
Bulgaria	43		
Japan	49		
Poland	11		
Russia	46		
Serbia	63		
Slovakia	19		
Ukraine	67		
United States	43		
Region of Enrollment Units: Subjects			
Europe	249		
Japan	49		
United States	43		
Baseline BMI Category Units: Subjects			
< 18.5 kg/m2	3		
18.5 - <25.0 kg/m2	146		
25.0 - <30.0 kg/m2	115		
>=30.0 kg/m2	77		
Baseline Weight (kg) Units: kg arithmetic mean standard deviation	- -		

Baseline CGI-BP-S Depression Score			
Measure Description: Clinical Global Impressions - Severity: Bipolar Version (CGI-BP-S) score (depression) is a single value, clinician-rated assessment of illness severity, and 7-point scale with range from 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; 7 = among the most extremely ill subjects. A higher score is associated with greater illness severity.			
Units: units on a scale arithmetic mean standard deviation	- -		
Baseline MADRS Total Score			
Measure Description: MADRS is a clinician-rated assessment of the subject's level of depression. The measure contains 10 items that measure apparent and reported sadness, inner tension, reduced sleep and appetite, difficulty concentrating, lassitude, inability to feel, and pessimistic and suicidal thoughts, each ranging from 0 to 6. The MADRS total score ranges from 0 to 60, with higher scores indicating increased depressive symptoms			
Units: units on a scale arithmetic mean standard deviation	- -		
Baseline BMI (kg/m^2) Units: kg/m^2 arithmetic mean standard deviation	- -		

End points

End points reporting groups

Reporting group title	SEP-4199 200 mg
Reporting group description: SEP-4199 200 mg/day (supplied in two 100mg tablets)	
Reporting group title	SEP-4199 400 mg
Reporting group description: SEP-4199 400 mg/day (supplied in two 200mg tablets)	
Reporting group title	Placebo
Reporting group description: Placebo (supplied in two tablets/day)	

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: MADRS is a clinician-rated assessment of the subject's level of depression. The measure contains 10 items that measure apparent and reported sadness, inner tension, reduced sleep and appetite, difficulty concentrating, lassitude, inability to feel, and pessimistic and suicidal thoughts, each ranging from 0 to 6. The MADRS total score ranges from 0 to 60, with higher scores indicating increased depressive symptoms	
End point type	Primary
End point timeframe: 6 Weeks	

End point values	SEP-4199 200 mg	SEP-4199 400 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	96[1]	97[2]	96[3]	
Units: units on a scale				
least squares mean (standard error)	-19.485 (± 1.226)	-19.324 (± 1.182)	-16.196 (± 1.231)	

Notes:

[1] - The analysis population was the ITT population, excluding subjects from Japan Region

[2] - The analysis population was the ITT population, excluding subjects from Japan Region

[3] - The analysis population was the ITT population, excluding subjects from Japan Region

Statistical analyses

Statistical analysis title	SEP-4199 400mg and Placebo
Comparison groups	SEP-4199 400 mg v Placebo

Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.051 [4]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-3.128
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.273
upper limit	0.017
Variability estimate	Standard error of the mean
Dispersion value	1.597

Notes:

[4] - nominal p-value

Statistical analysis title	SEP-4199 200mg and Placebo
Comparison groups	Placebo v SEP-4199 200 mg
Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.044 [5]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-3.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.489
upper limit	-0.09
Variability estimate	Standard error of the mean
Dispersion value	1.625

Notes:

[5] - nominal p-value

Secondary: Change from baseline in global severity assessed by the Clinical Global Impressions – Severity: Bipolar Version (CGI-BP-S) score (depression) at Week 6

End point title	Change from baseline in global severity assessed by the Clinical Global Impressions – Severity: Bipolar Version (CGI-BP-S) score (depression) at Week 6

End point description:

Clinical Global Impressions – Severity: Bipolar Version (CGI-BP-S) score (depression) is a single value, clinician-rated assessment of illness severity, and 7-point scale with range from 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; 7 = among the most extremely ill subjects. A higher score is associated with greater illness severity.

End point type	Secondary

End point timeframe:

6 Weeks

End point values	SEP-4199 200 mg	SEP-4199 400 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	96[6]	97[7]	96[8]	
Units: units on a scale				
least squares mean (standard error)	-2.020 (± 0.144)	-1.958 (± 0.138)	-1.739 (± 0.144)	

Notes:

[6] - The analysis population was the ITT population, excluding subjects from Japan Region

[7] - The analysis population was the ITT population, excluding subjects from Japan Region

[8] - The analysis population was the ITT population, excluding subjects from Japan Region

Statistical analyses

Statistical analysis title	SEP-4199 400mg and Placebo
Comparison groups	SEP-4199 400 mg v Placebo
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.243 [9]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.219
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.588
upper limit	0.15
Variability estimate	Standard error of the mean
Dispersion value	0.187

Notes:

[9] - nominal p-value

Statistical analysis title	SEP-4199 200mg and Placebo
Comparison groups	SEP-4199 200 mg v Placebo
Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.143 [10]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.281
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.658
upper limit	0.095

Variability estimate	Standard error of the mean
Dispersion value	0.191

Notes:

[10] - nominal p-value

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were untoward medical occurrences that occurred on or after the first dose of study medication.
Up to 7 weeks

Adverse event reporting additional description:

Adverse events were untoward medical occurrences that occurred on or after the first dose of study medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	SEP-4199 200 mg

Reporting group description:

SEP-4199 200 mg/day (supplied in two 100mg tablets)

Reporting group title	Placebo

Reporting group description:

Placebo (supplied in two tablets/day)

Reporting group title	SEP-4199 400 mg

Reporting group description:

SEP-4199 400 mg/day (supplied in two 200mg tablets)

Serious adverse events	SEP-4199 200 mg	Placebo	SEP-4199 400 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 113 (0.88%)	1 / 114 (0.88%)	0 / 114 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Foot fracture			
subjects affected / exposed	0 / 113 (0.00%)	1 / 114 (0.88%)	0 / 114 (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
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	1 / 113 (0.88%)	0 / 114 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
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	SEP-4199 200 mg	Placebo	SEP-4199 400 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 113 (18.58%)	29 / 114 (25.44%)	23 / 114 (20.18%)
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 113 (0.00%)	0 / 114 (0.00%)	9 / 114 (7.89%)
occurrences (all)	0	0	9
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 113 (9.73%)	13 / 114 (11.40%)	3 / 114 (2.63%)
occurrences (all)	12	16	3
Psychiatric disorders			
Insomnia			
subjects affected / exposed	5 / 113 (4.42%)	7 / 114 (6.14%)	5 / 114 (4.39%)
occurrences (all)	6	9	6
Anxiety			
subjects affected / exposed	1 / 113 (0.88%)	7 / 114 (6.14%)	2 / 114 (1.75%)
occurrences (all)	2	7	5
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 113 (3.54%)	6 / 114 (5.26%)	4 / 114 (3.51%)
occurrences (all)	4	6	4

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