Clinical trial results:
A 4-Week, Randomized, Double-blind, Parallel-group, Placebo-controlled, Flexibly-dosed, Multicenter Study to Evaluate the Efficacy and Safety of SEP-363856 in Acutely Psychotic Adult Subjects With Schizophrenia

Summary

EudraCT number	2016-001555-41
Trial protocol	HU
Global end of trial date	31 July 2018

Results information

Result version number	v1 (current)
This version publication date	22 August 2019
First version publication date	22 August 2019

Trial information

Trial identification

Sponsor protocol code	SEP361-201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02969382
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sunovion Pharmaceuticals Inc.
Sponsor organisation address	84 Waterford Drive, Marlborough, United States, 01752
Public contact	CNS Medical Director, Sunovion Pharmaceuticals Inc., 01 001-866-503-6351, CLINICALTRIALDISCLOSURE@SUNOVION.COM
Scientific contact	CNS Medical Director, Sunovion Pharmaceuticals Inc., 01 001-866-503-6351, 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	31 July 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 July 2018
Global end of trial reached?	Yes
Global end of trial date	31 July 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of flexibly dosed SEP-363856 (50 or 75 mg/day) compared with placebo in acutely psychotic adult subjects with schizophrenia as measured by the Positive and Negative Syndrome Scale (PANSS).

Protection of trial subjects:

THE STUDY WAS CONDUCTED ACCORDING TO THE PROTOCOL, INTERNATIONAL COUNCIL FOR HARMONISATION (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	05 December 2016
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	Hungary: 12
Country: Number of subjects enrolled	Romania: 10
Country: Number of subjects enrolled	Russian Federation: 98
Country: Number of subjects enrolled	Ukraine: 73
Country: Number of subjects enrolled	United States: 52
Worldwide total number of subjects	245
EEA total number of subjects	22

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)	245
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Informed consent were obtained before any study procedures were performed. Subjects were evaluated for eligibility and tapered off all psychotropic medications (except as noted in the protocol) in a manner consistent with labeling recommendations and conventional medical practices. Subjects remained hospitalized during the screening period.

Pre-assignment period milestones

Number of subjects started	295[1]
Number of subjects completed	245

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Adverse event, non-fatal: 1
Reason: Number of subjects	Entry criteria not met: 39
Reason: Number of subjects	Consent withdrawn by subject: 8
Reason: Number of subjects	Other: 1
Reason: Number of subjects	Sponsor decision: 1

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 50 subjects never entered the trial because of screening faiure

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo capsule once daily

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

Dosage and administration details:

One capsule per day for 4 weeks

Arm title	SEP-363856

Arm description:

SEP-363856 capsule (50 mg or 75 mg) once daily

Arm type	Experimental

Investigational medicinal product name	SEP-363856
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One 50 mg capsule or one 75 mg capsule per day flexible dosing for 4 weeks

Number of subjects in period 1	Placebo	SEP-363856
Started	125	120
Completed	99	94
Not completed	26	26
Consent withdrawn by subject	14	9
Adverse event, non-fatal	8	10
Death	-	1
Lack of efficacy	4	5
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo capsule once daily	
Reporting group title	SEP-363856
Reporting group description:	
SEP-363856 capsule (50 mg or 75 mg) once daily	

Reporting group values	Placebo	SEP-363856	Total
Number of subjects	125	120	245
Age Categorical			
Units: Subjects			
In Utero	0	0	0
Pre-term newborn - gestational age < 37 wk	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)	125	120	245
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
Units: years			
arithmetic mean	30.6	30.0	
standard deviation	± 6.07	± 5.76	-
Gender Categorical			
Units: Subjects			
Female	46	43	89
Male	79	77	156
Age, Customized			
Units: Subjects			
>=18 - <25	29	26	55
>=25 - <=40	96	94	190
Baseline BMI Group			
Units: Subjects			
<18.5 kg/m^2	1	4	5
>=18.5 - <25.0 kg/m^2	70	59	129
>=25.0 - <30.0 kg/m^2	43	41	84
>=30.0 kg/m^2	11	16	27
Baseline Height (cm)			
Units: cm			
arithmetic mean	172.7	173.0	
standard deviation	± 7.78	± 8.50	-
Baseline Weight (kg)			
Units: kg			

arithmetic mean	73.74	75.23	
standard deviation	± 12.645	± 15.768	-
Baseline Body Mass Index (kg/m^2)			
Units: kg/m^2			
arithmetic mean	24.71	25.01	
standard deviation	± 3.727	± 4.238	-
Baseline Waist Circumference (cm)			
Units: cm			
arithmetic mean	84.18	85.21	
standard deviation	± 12.186	± 14.191	-

End points

End points reporting groups	
Reporting group title	Placebo
Reporting group description: Placebo capsule once daily	
Reporting group title	SEP-363856
Reporting group description: SEP-363856 capsule (50 mg or 75 mg) once daily	

Primary: Change from Baseline in PANSS total score at Week 4	
End point title	Change from Baseline in PANSS total score at Week 4
End point description:	
End point type	Primary
End point timeframe: Baseline, Week 4	

End point values	Placebo	SEP-363856		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	120		
Units: Units on a scale				
least squares mean (standard error)	-9.7 (± 1.61)	-17.2 (± 1.66)		

Statistical analyses

Statistical analysis title	Mixed Model for Repeated Measures (MMRM)
Comparison groups	Placebo v SEP-363856
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-7.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.9
upper limit	-3
Variability estimate	Standard error of the mean
Dispersion value	2.23

Secondary: Change from Baseline in CGI-S score at Week 4	
End point title	Change from Baseline in CGI-S score at Week 4
End point description:	
End point type	Secondary
End point timeframe:	
Baseline, Week 4	

End point values	Placebo	SEP-363856		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	120		
Units: Units on a scale				
least squares mean (standard error)	-0.5 (± 0.09)	-1.0 (± 0.09)		

Statistical analyses

Statistical analysis title	Mixed Model for Repeated Measures (MMRM)
Comparison groups	Placebo v SEP-363856
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	-0.2
Variability estimate	Standard error of the mean
Dispersion value	0.12

Secondary: Change from Baseline in PANSS Positive Subscale score at Week 4	
End point title	Change from Baseline in PANSS Positive Subscale score at Week 4
End point description:	
End point type	Secondary

End point timeframe: Baseline, Week 4

End point values	Placebo	SEP-363856		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	120		
Units: Units on a scale				
least squares mean (standard error)	-3.9 (± 0.51)	-5.5 (± 0.53)		

Statistical analyses

Statistical analysis title	Mixed Model for Repeated Measures (MMRM)
Comparison groups	Placebo v SEP-363856
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.019
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
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	0.71

Secondary: Change from Baseline in PANSS Negative Subscale score at Week 4	
End point title	Change from Baseline in PANSS Negative Subscale score at Week 4
End point description:	

End point type	Secondary
End point timeframe: Baseline, Week 4	

End point values	Placebo	SEP-363856		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	120		
Units: Units on a scale				
least squares mean (standard error)	-1.6 (± 0.41)	-3.1 (± 0.42)		

Statistical analyses

Statistical analysis title	Mixed Model for Repeated Measures (MMRM)
Comparison groups	Placebo v SEP-363856
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.008
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6
upper limit	-0.4
Variability estimate	Standard error of the mean
Dispersion value	0.55

Secondary: Change from Baseline in PANSS General Psychopathology Subscale score at Week 4

End point title	Change from Baseline in PANSS General Psychopathology Subscale score at Week 4
End point description:	

End point type	Secondary
End point timeframe:	
Baseline, Week 4	

End point values	Placebo	SEP-363856		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	120		
Units: Units on a scale				
least squares mean (standard error)	-4.7 (± 0.84)	-9.0 (± 0.87)		

Statistical analyses

Statistical analysis title	Mixed Model for Repeated Measures (MMRM)
Comparison groups	Placebo v SEP-363856
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-4.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.6
upper limit	-2
Variability estimate	Standard error of the mean
Dispersion value	1.15

Secondary: Change from Baseline in BNSS total score at Week 4

End point title	Change from Baseline in BNSS total score at Week 4
End point description:	
End point type	Secondary
End point timeframe:	
Baseline, Week 4	

End point values	Placebo	SEP-363856		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	113		
Units: Units on a scale				
least squares mean (standard error)	-2.7 (± 0.91)	-7.1 (± 0.95)		

Statistical analyses

Statistical analysis title	Mixed Model for Repeated Measures (MMRM)
Comparison groups	Placebo v SEP-363856
Number of subjects included in analysis	232
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-4.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.8
upper limit	-1.8
Variability estimate	Standard error of the mean
Dispersion value	1.26

Secondary: Change from Baseline in MADRS total score at Week 4

End point title	Change from Baseline in MADRS total score at Week 4
End point description:	
End point type	Secondary
End point timeframe:	
Baseline, Week 4	

End point values	Placebo	SEP-363856		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	120		
Units: Units on a scale				
least squares mean (standard error)	-1.6 (± 0.57)	-3.3 (± 0.59)		

Statistical analyses

Statistical analysis title	Mixed Model for Repeated Measures (MMRM)
Comparison groups	Placebo v SEP-363856
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	-0.3
Variability estimate	Standard error of the mean
Dispersion value	0.75

Secondary: PANSS response at Week 4, defined as a 20% or greater improvement from Baseline in PANSS total score

End point title	PANSS response at Week 4, defined as a 20% or greater improvement from Baseline in PANSS total score

End point description:

End point type	Secondary

End point timeframe:

Baseline, Week 4

End point values	Placebo	SEP-363856		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	96		
Units: Subjects	44	62		

Statistical analyses

Statistical analysis title	Logistic Regression
Comparison groups	Placebo v SEP-363856
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.645
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.422
upper limit	4.921

Secondary: Incidence of overall adverse events

End point title	Incidence of overall adverse events

End point description:

End point type	Secondary

End point timeframe:

From first dose of study drug to last study visit

End point values	Placebo	SEP-363856		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	120		
Units: Subjects	63	55		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of serious adverse events

End point title	Incidence of serious adverse events

End point description:

End point type	Secondary

End point timeframe:

From first dose of study drug to last study visit

End point values	Placebo	SEP-363856		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	120		
Units: Subjects	3	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of adverse events leading to discontinuation of study drug

End point title	Incidence of adverse events leading to discontinuation of study drug

End point description:

End point type	Secondary

End point timeframe:

From first dose of study drug to last study visit

End point values	Placebo	SEP-363856		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	120		
Units: Subjects	8	10		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of adverse events leading to discontinuation from study

End point title	Incidence of adverse events leading to discontinuation from study

End point description:

End point type	Secondary

End point timeframe:

From first dose of study drug to last study visit

End point values	Placebo	SEP-363856		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	120		
Units: Subjects	8	11		

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of subjects with suicidal ideation using the C-SSRS

End point title	Frequency of subjects with suicidal ideation using the C-SSRS

End point description:

End point type	Secondary

End point timeframe:

Overall post-Baseline double-blind treatment period

End point values	Placebo	SEP-363856		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	120		
Units: Subjects	2	0		

Statistical analyses

Statistical analysis title	Fisher's Exact Test
Comparison groups	Placebo v SEP-363856
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.498
Method	Fisher exact

Secondary: Frequency of subjects with suicidal behavior using the C-SSRS

End point title	Frequency of subjects with suicidal behavior using the C-SSRS

End point description:

End point type	Secondary

End point timeframe:

Overall post-Baseline double-blind treatment period

End point values	Placebo	SEP-363856		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	120		
Units: Subjects	1	0		

Statistical analyses

Statistical analysis title	Fisher's Exact Test
Comparison groups	Placebo v SEP-363856
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.999
Method	Fisher exact

Secondary: Frequency of subjects with suicidality using the C-SSRS

End point title	Frequency of subjects with suicidality using the C-SSRS

End point description:

End point type	Secondary

End point timeframe:

Overall post-Baseline double-blind treatment period

End point values	Placebo	SEP-363856		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	120		
Units: Subjects	2	0		

Statistical analyses

Statistical analysis title	Fisher's Exact Test
Comparison groups	Placebo v SEP-363856
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.498
Method	Fisher exact

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 5 weeks (from first dose of study drug to last study visit)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	Placebo
Reporting group description: Placebo capsule once daily	
Reporting group title	SEP-363856
Reporting group description: SEP-363856 capsule (50 mg or 75 mg) once daily	

Serious adverse events	Placebo	SEP-363856	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 125 (2.40%)	2 / 120 (1.67%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	1	
Cardiac disorders			
Cardiovascular insufficiency			
subjects affected / exposed	0 / 125 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Psychiatric disorders			
Schizophrenia			
subjects affected / exposed	3 / 125 (2.40%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide Attempt			
subjects affected / exposed	1 / 125 (0.80%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	SEP-363856	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 125 (37.60%)	35 / 120 (29.17%)	
Nervous system disorders			
Somnolence			
subjects affected / exposed	6 / 125 (4.80%)	8 / 120 (6.67%)	
occurrences (all)	6	8	
Headache			
subjects affected / exposed	15 / 125 (12.00%)	11 / 120 (9.17%)	
occurrences (all)	18	15	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	4 / 125 (3.20%)	6 / 120 (5.00%)	
occurrences (all)	4	7	
Psychiatric disorders			
Agitation			
subjects affected / exposed	6 / 125 (4.80%)	6 / 120 (5.00%)	
occurrences (all)	6	6	
Anxiety			
subjects affected / exposed	9 / 125 (7.20%)	2 / 120 (1.67%)	
occurrences (all)	12	2	
Insomnia			
subjects affected / exposed	13 / 125 (10.40%)	4 / 120 (3.33%)	
occurrences (all)	20	5	
Schizophrenia			
subjects affected / exposed	7 / 125 (5.60%)	7 / 120 (5.83%)	
occurrences (all)	8	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 March 2017	The following major changes/clarifications, including Nonsubstantial Amendment 1 (08 Sep 2016) and Nonsubstantial Amendment 2 (07 Oct 2016) were included in the Version 3.00 protocol: • Clarified that the DEQ was designed to assess subjective effects only. • Clarified that subjects would remain hospitalized for the duration of the screening/washout period. • Clarified inclusion criteria for acute exacerbation of psychotic symptoms and prior hospitalizations. • Clarified exclusion criterion for antipsychotic medications less than 2 weeks in duration and removed exclusion criterion for subjects with past episodes of significant extrapyramidal symptoms (EPS). • Added PANSS randomization criteria. • If a subject was issued a day pass, an unscheduled urine drug screen upon returning to the site was added. • Added unscheduled collection of SAS, BARS, and AIMS scales if a subject developed EPS requiring treatment. • Clarified prior medications washout for clozapine; added zopiclone as a permitted medication at the discretion of the Investigator; removed codeine, hydrocodone, and methadone as prohibited medications; and clarified that all concomitant antipsychotic medications were prohibited. • Clarified that subjects were allowed 7 days to stabilize in hospital if they did not meet discharge criteria at Visit 7 or early termination. • Updated the order of assessments so that C-SSRS is performed before the CGI-S and that visit day study drug administration occurred after completion of scale assessments.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported