Clinical trial results:
A 26-Week Open-label Safety and Tolerability Extension Study of SEP-363856 in Adult Subjects with Schizophrenia

Summary

EudraCT number	2016-001556-21
Trial protocol	HU
Global end of trial date	29 January 2019

Results information

Result version number	v1
This version publication date	14 February 2020
First version publication date	14 February 2020

Trial information

Trial identification

Sponsor protocol code	SEP361-202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02970929
WHO universal trial number (UTN)	-

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., +1 866-503-6351, clinicaltrialdisclosure@sunovion.com
Scientific contact	CNS Medical Director, Sunovion Pharmaceuticals Inc., +1 866-503-6351, 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	29 January 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 January 2019
Global end of trial reached?	Yes
Global end of trial date	29 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the long-term safety and tolerability of flexibly dosed SEP-363856 (25, 50, or 75 mg/day [ie, once daily]) in adult subjects with schizophrenia who have completed Study SEP361-201 by the incidence of overall adverse events (AEs), serious AEs (SAEs), and AEs leading to discontinuation.

Protection of trial subjects:

This 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	31 January 2017
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: 8
Country: Number of subjects enrolled	Romania: 6
Country: Number of subjects enrolled	Russian Federation: 68
Country: Number of subjects enrolled	Ukraine: 54
Country: Number of subjects enrolled	United States: 20
Worldwide total number of subjects	156
EEA total number of subjects	14

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)	156
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 157 subjects rolled over from SEP361-201 to the current study. One subject was not dosed and thus excluded from the analysis population. The data on the 156 dosed subjects are presented in the form.

Pre-assignment

Screening details:

Subjects must have completed the 4 week double-blind treatment phase of Study SEP361-201 to enter this study.

Period 1

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

Blinding implementation details:

This study was open-label. No blinding was implemented.

Arms

Arm title	SEP-363856

Arm description:

SEP-363856 capsule (25 mg, 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:

SEP-363856 capsule (25 mg, 50 mg, or 75 mg) once daily

Number of subjects in period 1	SEP-363856
Started	156
Completed	105
Not completed	51
Consent withdrawn by subject	16
Adverse event, non-fatal	18
Other	8
non-compliance with study drug	1
Lack of efficacy	8

Baseline characteristics

Reporting groups	
Reporting group title	SEP-363856
Reporting group description:	
SEP-363856 capsule (25 mg, 50 mg, or 75 mg) once daily	

Reporting group values	SEP-363856	Total	
Number of subjects	156	156	
Age Categorical Units: Participants			
<=18 years	2	2	
Between 18 and 65 years	154	154	
>=65 years	0	0	
Age Continuous Units: years			
arithmetic mean	30.2		
standard deviation	± 6.03	-	
Gender, Male/Female Units: Participants			
Female	54	54	
Male	102	102	
Age, Customized Units: Subjects			
>=18 - <25 years	38	38	
>=25 - <=40 years	118	118	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	4	4	
Asian	0	0	
Black or African American	15	15	
More than one race	1	1	
Native Hawaiian or Other Pacific Islander	0	0	
Unknown or Not Reported	0	0	
White	136	136	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	5	5	
Not Hispanic or Latino	151	151	
Unknown or Not Reported	0	0	
Country Units: Subjects			
Hungary	8	8	
Romania	6	6	
Russia	68	68	
Ukraine	54	54	
United States	20	20	
Region of Enrollment			

Units: Subjects			
Non-US	136	136	
United States	20	20	
DB Baseline BMI Group Units: Subjects			
<18.5 kg/m^2	2	2	
>=18.5 - <25.0 kg/m^2	80	80	
>=25.0 - <30.0 kg/m^2	55	55	
>=30.0 kg/m^2	19	19	
OL Baseline BMI Group Units: Subjects			
<18.5 kg/m^2	3	3	
>=18.5 - <25.0 kg/m^2	82	82	
>=25.0 - <30.0 kg/m^2	53	53	
>=30.0 kg/m^2	18	18	
DB Baseline Height (cm) Units: cm			
arithmetic mean	173.1		
standard deviation	± 7.73	-	
DB Baseline Weight (kg) Units: kg			
arithmetic mean	75.38		
standard deviation	± 13.873	-	
DB Baseline Body Mass Index (kg/m^2) Units: kg/m^2			
arithmetic mean	25.07		
standard deviation	± 3.863	-	
DB Baseline Waist Circumference (cm) Units: cm			
arithmetic mean	85.36		
standard deviation	± 13.508	-	
OL Baseline Height (cm) Units: cm			
arithmetic mean	173.1		
standard deviation	± 7.73	-	
OL Baseline Weight (kg) Units: kg			
arithmetic mean	75.32		
standard deviation	± 13.987	-	
OL Baseline Body Mass Index (kg/m^2) Units: kg/m^2			
arithmetic mean	25.05		
standard deviation	± 3.890	-	
OL Baseline Waist Circumference (cm) Units: cm			
arithmetic mean	85.20		
standard deviation	± 13.467	-	

Subject analysis sets	
Subject analysis set title	PBO-SEP
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects who received Placebo in study SEP361-201 and SEP-363856 in study SEP361-202	
Subject analysis set title	SEP-SEP
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects who received SEP-363856 in study SEP361-201 and SEP-363856 in study SEP361-202	

Reporting group values	PBO-SEP	SEP-SEP	
Number of subjects	79	77	
Age Categorical Units: Participants			
<=18 years	2	0	
Between 18 and 65 years	77	77	
>=65 years	0	0	
Age Continuous Units: years			
arithmetic mean	30.2	30.2	
standard deviation	± 6.37	± 5.70	
Gender, Male/Female Units: Participants			
Female	29	25	
Male	50	52	
Age, Customized Units: Subjects			
>=18 - <25 years	21	17	
>=25 - <=40 years	58	60	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	3	
Asian	0	0	
Black or African American	5	10	
More than one race	0	1	
Native Hawaiian or Other Pacific Islander	0	0	
Unknown or Not Reported	0	0	
White	73	63	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	4	1	
Not Hispanic or Latino	75	76	
Unknown or Not Reported	0	0	
Country Units: Subjects			
Hungary	5	3	
Romania	3	3	
Russia	36	32	
Ukraine	29	25	
United States	6	14	

Region of Enrollment Units: Subjects			
Non-US	73	63	
United States	6	14	
DB Baseline BMI Group Units: Subjects			
<18.5 kg/m^2	1	1	
>=18.5 - <25.0 kg/m^2	46	34	
>=25.0 - <30.0 kg/m^2	27	28	
>=30.0 kg/m^2	5	14	
OL Baseline BMI Group Units: Subjects			
<18.5 kg/m^2	2	1	
>=18.5 - <25.0 kg/m^2	48	34	
>=25.0 - <30.0 kg/m^2	25	28	
>=30.0 kg/m^2	4	14	
DB Baseline Height (cm) Units: cm			
arithmetic mean	173.2	173.0	
standard deviation	± 7.53	± 7.98	
DB Baseline Weight (kg) Units: kg			
arithmetic mean	73.14	77.68	
standard deviation	± 10.849	± 16.159	
DB Baseline Body Mass Index (kg/m^2) Units: kg/m^2			
arithmetic mean	24.36	25.80	
standard deviation	± 3.221	± 4.328	
DB Baseline Waist Circumference (cm) Units: cm			
arithmetic mean	83.68	87.08	
standard deviation	± 11.612	± 15.093	
OL Baseline Height (cm) Units: cm			
arithmetic mean	173.2	173.0	
standard deviation	± 7.53	± 7.98	
OL Baseline Weight (kg) Units: kg			
arithmetic mean	72.83	77.88	
standard deviation	± 10.968	± 16.200	
OL Baseline Body Mass Index (kg/m^2) Units: kg/m^2			
arithmetic mean	24.25	25.87	
standard deviation	± 3.213	± 4.350	
OL Baseline Waist Circumference (cm) Units: cm			
arithmetic mean	83.01	87.44	
standard deviation	± 11.764	± 14.759	

End points

End points reporting groups

Reporting group title	SEP-363856
Reporting group description:	
SEP-363856 capsule (25 mg, 50 mg, or 75 mg) once daily	
Subject analysis set title	PBO-SEP
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects who received Placebo in study SEP361-201 and SEP-363856 in study SEP361-202	
Subject analysis set title	SEP-SEP
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects who received SEP-363856 in study SEP361-201 and SEP-363856 in study SEP361-202	

Primary: The incidence of overall Adverse Events (AEs), Serious Adverse Events (SAEs), and Adverse Events (AEs) leading to discontinuation

End point title	The incidence of overall Adverse Events (AEs), Serious Adverse Events (SAEs), and Adverse Events (AEs) leading to discontinuation[1]
End point description:	
End point type	Primary
End point timeframe:	
From first dose of study drug to last study visit (27 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: This study was an open label study no statistical analysis was performed

End point values	SEP-363856			
Subject group type	Reporting group			
Number of subjects analysed	156			
Units: Participants				
All Adverse Events	88			
Serious Adverse Events	15			
Adverse Events Leading to Discontinuation	18			
Adverse Events Discontinuation of study medication	18			

Statistical analyses

No statistical analyses for this end point

Secondary: Severity of suicidal ideation and suicidal behavior using the Columbia – Suicide Severity Rating Scale (C-SSRS)

End point title	Severity of suicidal ideation and suicidal behavior using the Columbia – Suicide Severity Rating Scale (C-SSRS)

End point description:

End point type	Secondary

End point timeframe:

Overall post-OL Baseline treatment period (26 weeks)

End point values	SEP-363856			
Subject group type	Reporting group			
Number of subjects analysed	156[2]			
Units: Participants				
SI: Wish to be dead	2			
SI: Non-specific active suicidal thoughts	2			
SI: Any methods (not plan) without intent to act	0			
SI: Some intent to act, without specific plan	0			
SI: Specific plan and intent	0			
SB: Preparatory acts or behavior	0			
SB: Aborted attempt	1			
SB: Interrupted attempt	0			
SB: Actual attempt (non-fatal)	0			
SB: Completed suicide	0			

Notes:

[2] - SI: Suicidal ideation.
SB: Suicidal behavior.

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of suicidal ideation and suicidal behavior using the Columbia – Suicide Severity Rating Scale (C-SSRS)

End point title	Frequency of suicidal ideation and suicidal behavior using the Columbia – Suicide Severity Rating Scale (C-SSRS)

End point description:

End point type	Secondary

End point timeframe:

Overall post-OL Baseline treatment period (26 weeks)

End point values	SEP-363856			
Subject group type	Reporting group			
Number of subjects analysed	156			
Units: Participants				
Any suicidal ideation	3			
Any suicidal behavior	1			
Any suicidality	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of relapse during the 26-week OL period for subjects who demonstrated a clinical response to 4 weeks of treatment with SEP-363856

End point title	Rate of relapse during the 26-week OL period for subjects who demonstrated a clinical response to 4 weeks of treatment with SEP-363856

End point description:

Relapse is defined as the earliest occurrence of any of the following: - An increase in PANSS total score by ≥ 30% from the PANSS total score at clinical response and a CGI-S score ≥ 3 - Re-hospitalization for worsening of psychosis - Emergence of suicidality, homicidality, and/or risk of harm to self or others

End point type	Secondary

End point timeframe:

From the time of clinical response to relapse or censor (one day after the last study drug dose)

End point values	PBO-SEP	SEP-SEP		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	59[3]	51[4]		
Units: Participants	12	11		

Notes:

[3] - Subjects demonstrating clinical response to 4-week treatment with SEP-363856 included in analysis.
[4] - Subjects demonstrating clinical response to 4-week treatment with SEP-363856 included in analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Changes from DB Baseline of Study SEP361-201 and OL Baseline of Study SEP361-202 in Positive and Negative Syndrome Scale (PANSS) total score and subscale scores (positive, negative, and general psychopathology)

End point title	Changes from DB Baseline of Study SEP361-201 and OL Baseline of Study SEP361-202 in Positive and Negative Syndrome Scale (PANSS) total score and subscale scores (positive, negative, and general psychopathology)

End point description:

End point type	Secondary

End point timeframe:

DB Baseline, OL Baseline, Week 26

End point values	SEP-363856			
Subject group type	Reporting group			
Number of subjects analysed	156[5]			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Total Score: DB BLN Observed	101.5 (± 7.99)			
Total Score: OL BLN Observed	83.1 (± 15.03)			
Total Score: Wk 26 Observed	59.3 (± 12.45)			
Total Score: Chg from DB BLN at Wk 26	-41.8 (± 13.98)			
Total Score: Chg from OL BLN at Wk 26	-22.6 (± 15.48)			
Positive SS: DB BLN Observed	25.7 (± 3.22)			
Positive SS: OL BLN Observed	19.8 (± 4.96)			
Positive SS: Wk 26 Observed	12.2 (± 3.72)			
Positive SS: Chg from DB BLN at Wk 26	-13.5 (± 4.75)			
Positive SS: Chg from OL BLN at Wk 26	-7.3 (± 5.37)			
Negative SS: DB BLN Observed	25.4 (± 4.03)			
Negative SS: OL BLN Observed	22.3 (± 4.38)			
Negative SS: Wk 26 Observed	17.2 (± 4.10)			
Negative SS: Chg from DB BLN at Wk 26	-8.4 (± 4.48)			
Negative SS: Chg from OL BLN at Wk 26	-5.2 (± 4.20)			
Gen-Psychopathology SS: DB BLN Observed	50.4 (± 5.01)			
Gen-Psychopathology SS: OL BLN Observed	41.1 (± 7.93)			
Gen-Psychopathology SS: Wk 26 Observed	30.0 (± 6.77)			
Gen-Psychopathology SS: Chg from DB BLN at Wk 26	-19.9 (± 7.86)			
Gen-Psychopathology SS: Chg from OL BLN at Wk 26	-10.2 (± 8.31)			

Notes:

[5] - Subjects with missing PANSS data did not contribute to summary.
SS: Subscale Score. Gen: General.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from DB Baseline of Study SEP361-201 and OL Baseline of Study SEP361-202 in Clinical Global Impression - Severity (CGI-S) score

End point title	Change from DB Baseline of Study SEP361-201 and OL Baseline of Study SEP361-202 in Clinical Global Impression - Severity (CGI-S) score

End point description:

End point type	Secondary

End point timeframe:

DB Baseline, OL Baseline, Week 26

End point values	SEP-363856			
Subject group type	Reporting group			
Number of subjects analysed	156[6]			
Units: Units on a scale				
arithmetic mean (standard deviation)				
CGI-S Score: DB Baseline Observed	5.0 (± 0.42)			
CGI-S Score: OL Baseline Observed	4.0 (± 0.84)			
CGI-S Score: Week 26 Observed	3.0 (± 0.74)			
CGI-S Score: Change from DB Baseline at Week 26	-2.0 (± 0.82)			
CGI-S Score: Change from OL Baseline at Week 26	-1.0 (± 0.91)			

Notes:

[6] - Subjects with missing CGI-S score data did not contribute to the summary.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from DB Baseline of Study SEP361-201 and OL Baseline of Study SEP361-202 in Brief Negative Symptom Scale (BNSS) total score

End point title	Change from DB Baseline of Study SEP361-201 and OL Baseline of Study SEP361-202 in Brief Negative Symptom Scale (BNSS) total score

End point description:

End point type	Secondary

End point timeframe:

DB Baseline, OL Baseline, Week 26

End point values	SEP-363856			
Subject group type	Reporting group			
Number of subjects analysed	156[7]			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Total Score: DB Baseline Observed	38.4 (± 11.94)			
Total Score: OL Baseline Observed	33.0 (± 11.41)			
Total Score: Week 26 Observed	22.5 (± 11.83)			
Total Score: Change from DB Baseline at Week 26	-16.8 (± 12.42)			
Total Score: Change from OL Baseline at Week 26	-11.3 (± 9.69)			

Notes:

[7] - Subjects with missing BNSS score data did not contribute to the summary.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from DB Baseline of Study SEP361-201 and OL Baseline of Study SEP361-202 in Montgomery-Asberg Depression Rating Scale (MADRS) total score

End point title	Change from DB Baseline of Study SEP361-201 and OL Baseline of Study SEP361-202 in Montgomery-Asberg Depression Rating Scale (MADRS) total score

End point description:

End point type	Secondary

End point timeframe:

DB Baseline, OL Baseline, Week 26

End point values	SEP-363856			
Subject group type	Reporting group			
Number of subjects analysed	156[8]			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Total Score: DB Baseline Observed	12.6 (± 7.25)			
Total Score: OL Baseline Observed	9.2 (± 6.33)			
Total Score: Week 26 Observed	4.4 (± 4.72)			
Total Score: Change from DB Baseline at Week 26	-8.1 (± 6.44)			
Total Score: Change from OL Baseline at Week 26	-4.5 (± 5.28)			

Notes:

[8] - Subjects with missing MADRS data did not contribute to summary.

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects who achieved a response, defined as a 20% or greater improvement in PANSS total score from DB Baseline of Study SEP361-201

End point title	Proportion of subjects who achieved a response, defined as a 20% or greater improvement in PANSS total score from DB Baseline of Study SEP361-201

End point description:

End point type	Secondary

End point timeframe:

Week 26

End point values	PBO-SEP	SEP-SEP		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	53[9]	51[10]		
Units: Participants				
number (not applicable)	52	49		

Notes:

[9] - Subjects with PANSS total score data available at DB Baseline and Week 26 are included in analysis.

[10] - Subjects with PANSS total score data available at DB Baseline and Week 26 are included in analysis.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first dose of study drug to last study visit (27 weeks)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	SEP-363856
Reporting group description:	
SEP-363856 capsule (25 mg, 50 mg, or 75 mg) once daily	

Serious adverse events	SEP-363856		
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 156 (9.62%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Reproductive system and breast disorders			
Uterine haemorrhage			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 156 (0.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Acute psychosis			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 156 (0.64%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Depression			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 156 (0.64%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychotic disorder			

alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 156 (0.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Schizophrenia			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	11 / 156 (7.05%)		
occurrences causally related to treatment / all	2 / 11		
deaths causally related to treatment / all	0 / 0		
Suicidal ideation			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 156 (0.64%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	SEP-363856		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 156 (25.00%)		
Nervous system disorders			
Headache			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	18 / 156 (11.54%)		
occurrences (all)	36		
Psychiatric disorders			
Anxiety			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	8 / 156 (5.13%)		
occurrences (all)	36		
Insomnia			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	13 / 156 (8.33%)		
occurrences (all)	24		

Schizophrenia alternative dictionary used: MedDRA 19.0 subjects affected / exposed occurrences (all)	10 / 156 (6.41%) 12		

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