Clinical trial results:
A Randomized, Double-blind, Parallel-group, Placebo-controlled, Fixed-dose, Multicenter Study to Evaluate the Efficacy and Safety of SEP-363856 in Acutely Psychotic Subjects with Schizophrenia

Summary

EudraCT number	2019-000697-37
Trial protocol	LV HR
Global end of trial date	14 June 2023

Results information

Result version number	v1 (current)
This version publication date	15 June 2024
First version publication date	15 June 2024

Trial information

Trial identification

Sponsor protocol code	SEP361-302

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Sumitomo Pharma America, Inc.
Sponsor organisation address	84 Waterford Drive, Marlborough, United States,
Public contact	CNS Medical Director, Sumitomo Pharma America, Inc., +1 866-503-6351, ClinicalTrialDisclosure@sunovion.com
Scientific contact	CNS Medical Director, Sumitomo Pharma America, Inc., +1 866-503-6351, ClinicalTrialDisclosure@sunovion.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	
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	14 June 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 June 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of fixed doses of SEP-363856 (75 and 100 mg/day) compared with placebo in acutely psychotic adult subjects with schizophrenia as measured by the Positive and Negative Syndrome Scale (PANSS) total score.

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	08 October 2019
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 147
Country: Number of subjects enrolled	Bulgaria: 21
Country: Number of subjects enrolled	Colombia: 4
Country: Number of subjects enrolled	Croatia: 3
Country: Number of subjects enrolled	Latvia: 6
Country: Number of subjects enrolled	Russian Federation: 85
Country: Number of subjects enrolled	Serbia: 133
Country: Number of subjects enrolled	Ukraine: 65
Worldwide total number of subjects	464
EEA total number of subjects	30

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)	463
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects were evaluated for eligibility during a screening phase of up to 14 days, during which they were tapered off all psychotropic medications in a manner that was consistent with labeling recommendations and conventional medical practices. Subjects may be hospitalized during the screening/washout period at the discretion of the Investigator.

Pre-assignment period milestones

Number of subjects started	660[1]
Number of subjects completed	464

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Adverse event, non-fatal: 2
Reason: Number of subjects	Entry Criteria Not Met: 141
Reason: Number of subjects	Consent withdrawn by subject: 33
Reason: Number of subjects	Sponsor Decision: 13
Reason: Number of subjects	Other: 7

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: 196 subjects never entered the trial because of screening failure

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, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

One tablet daily

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:

One tablet per day for 6 weeks

Arm title	SEP-363856 75 mg/day

Arm description:

One tablet daily

Arm type	Experimental

Investigational medicinal product name	SEP-363856 75 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Peritumoral use, Oral use

Dosage and administration details:

One 50 mg tablet per day on Days 1-3, then one 75 mg tablet per day on Days 4-42

Arm title	SEP-363856 100 mg/day

Arm description:

One tablet daily

Arm type	Experimental
Investigational medicinal product name	SEP-363856 100 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One 50 mg tablet per day on Days 1-3, one 75 mg tablet per day on Days 4-7, then one 100 mg tablet per day on Days 8-42

Number of subjects in period 1	Placebo	SEP-363856 75 mg/day	SEP-363856 100 mg/day
Started	155	155	154
Completed	128	121	116
Not completed	27	34	38
Consent withdrawn by subject	14	14	15
Adverse event, non-fatal	10	14	19
Other	2	1	1
Lack of efficacy	1	5	3

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
One tablet daily	
Reporting group title	SEP-363856 75 mg/day
Reporting group description:	
One tablet daily	
Reporting group title	SEP-363856 100 mg/day
Reporting group description:	
One tablet daily	

Reporting group values	Placebo	SEP-363856 75 mg/day	SEP-363856 100 mg/day
Number of subjects	155	155	154
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)	155	155	153
From 65-84 years	0	0	1
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	38.6	38.5	37.5
standard deviation	± 10.82	± 11.24	± 10.33
Gender Categorical Units: Subjects			
Female	65	71	56
Male	90	84	98
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	3	0	1
Black or African American	39	33	40
Native Hawaiian or Other Pacific Islander	3	1	3
White	108	118	108
Multiracial	0	1	0
Other	2	2	2
Ethnicity Units: Subjects			
Hispanic or Latino	6	14	7

Not Hispanic or Latino	149	141	147
Country Units: Subjects			
United States	49	50	48
Bulgaria	6	7	8
Colombia	1	2	1
Croatia	2	0	1
Latvia	2	2	2
Russia	29	28	28
Serbia	45	44	44
Ukraine	21	22	22
Baseline CGI-S score Units: Units on a scale			
arithmetic mean	5.05	5.02	4.99
standard deviation	± 0.438	± 0.503	± 0.518
Baseline PANSS total score Units: Units on a scale			
arithmetic mean	100.2	101.0	100.0
standard deviation	± 8.23	± 10.50	± 9.28

Reporting group values	Total		
Number of subjects	464		
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)	463		
From 65-84 years	1		
85 years and over	0		
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender Categorical Units: Subjects			
Female	192		
Male	272		
Race Units: Subjects			
American Indian or Alaska Native	0		
Asian	4		
Black or African American	112		
Native Hawaiian or Other Pacific Islander	7		
White	334		
Multiracial	1		

Other	6		
Ethnicity Units: Subjects			
Hispanic or Latino	27		
Not Hispanic or Latino	437		
Country Units: Subjects			
United States	147		
Bulgaria	21		
Colombia	4		
Croatia	3		
Latvia	6		
Russia	85		
Serbia	133		
Ukraine	65		
Baseline CGI-S score Units: Units on a scale arithmetic mean standard deviation	 -		
Baseline PANSS total score Units: Units on a scale arithmetic mean standard deviation	 -		

End points

End points reporting groups	
Reporting group title	Placebo
Reporting group description: One tablet daily	
Reporting group title	SEP-363856 75 mg/day
Reporting group description: One tablet daily	
Reporting group title	SEP-363856 100 mg/day
Reporting group description: One tablet daily	

Primary: Change from Baseline in PANSS total score at Endpoint (Week 6)	
End point title	Change from Baseline in PANSS total score at Endpoint (Week 6)
End point description:	
End point type	Primary
End point timeframe: Baseline, Week 6	

End point values	Placebo	SEP-363856 75 mg/day	SEP-363856 100 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	155	153	152	
Units: Units on a scale				
least squares mean (standard error)	-14.3 (± 1.47)	-16.4 (± 1.49)	-18.1 (± 1.50)	

Statistical analyses

Statistical analysis title	Mixed Model for Repeated Measures (MMRM)
Comparison groups	Placebo v SEP-363856 100 mg/day
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.041 [1]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-3.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.5
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	1.86

Notes:

[1] - Nominal, 2-sided p-value presented

Statistical analysis title	Mixed Model for Repeated Measures (MMRM)
Comparison groups	Placebo v SEP-363856 75 mg/day
Number of subjects included in analysis	308
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.259 [2]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.7
upper limit	1.5
Variability estimate	Standard error of the mean
Dispersion value	1.85

Notes:

[2] - Nominal, 2-sided p-value presented

Secondary: Change from Baseline in CGI-S score at Endpoint (Week 6)

End point title	Change from Baseline in CGI-S score at Endpoint (Week 6)

End point description:

End point type	Secondary

End point timeframe:

Baseline, Week 6

End point values	Placebo	SEP-363856 75 mg/day	SEP-363856 100 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	155	152	152	
Units: Units on a scale				
least squares mean (standard error)	-0.78 (± 0.088)	-0.91 (± 0.089)	-0.93 (± 0.090)	

Statistical analyses

Statistical analysis title	Mixed Model for Repeated Measures (MMRM)
Comparison groups	Placebo v SEP-363856 100 mg/day
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.172
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.37
upper limit	0.07
Variability estimate	Standard error of the mean
Dispersion value	0.112

Statistical analysis title	Mixed Model for Repeated Measures (MMRM)
Comparison groups	Placebo v SEP-363856 75 mg/day
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.219 [3]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.36
upper limit	0.08
Variability estimate	Standard error of the mean
Dispersion value	0.111

Notes:

[3] - Nominal, 2-sided p-value reported

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 7 weeks (from first dose of study drug to last study visit)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups	
Reporting group title	Placebo
Reporting group description: One tablet daily	
Reporting group title	SEP-363856 100 mg/day
Reporting group description: One tablet daily	
Reporting group title	SEP-363856 75 mg/day
Reporting group description: One tablet daily	

Serious adverse events	Placebo	SEP-363856 100 mg/day	SEP-363856 75 mg/day
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 155 (3.87%)	11 / 154 (7.14%)	14 / 155 (9.03%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Coronavirus test positive			
subjects affected / exposed	1 / 155 (0.65%)	0 / 154 (0.00%)	0 / 155 (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
Injury, poisoning and procedural complications			
Toxicity to various agents			
subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	0 / 155 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Food poisoning			

subjects affected / exposed	0 / 155 (0.00%)	0 / 154 (0.00%)	1 / 155 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Schizophrenia			
subjects affected / exposed	4 / 155 (2.58%)	9 / 154 (5.84%)	13 / 155 (8.39%)
occurrences causally related to treatment / all	1 / 4	2 / 9	2 / 13
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant catatonia			
subjects affected / exposed	0 / 155 (0.00%)	0 / 154 (0.00%)	1 / 155 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Rhabdomyolysis			
subjects affected / exposed	0 / 155 (0.00%)	0 / 154 (0.00%)	1 / 155 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Corona virus infection			
subjects affected / exposed	1 / 155 (0.65%)	1 / 154 (0.65%)	0 / 155 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	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	Placebo	SEP-363856 100 mg/day	SEP-363856 75 mg/day
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 155 (23.23%)	52 / 154 (33.77%)	53 / 155 (34.19%)
Nervous system disorders			
Headache			
subjects affected / exposed	14 / 155 (9.03%)	17 / 154 (11.04%)	18 / 155 (11.61%)
occurrences (all)	17	18	22
Psychiatric disorders			
Insomnia			

subjects affected / exposed	9 / 155 (5.81%)	13 / 154 (8.44%)	15 / 155 (9.68%)
occurrences (all)	13	13	18
Schizophrenia			
subjects affected / exposed	7 / 155 (4.52%)	13 / 154 (8.44%)	11 / 155 (7.10%)
occurrences (all)	7	15	11
Agitation			
subjects affected / exposed	8 / 155 (5.16%)	5 / 154 (3.25%)	9 / 155 (5.81%)
occurrences (all)	10	7	21
Anxiety			
subjects affected / exposed	6 / 155 (3.87%)	12 / 154 (7.79%)	17 / 155 (10.97%)
occurrences (all)	10	17	23

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 September 2020	Protocol Ver1.00 (24Apr2019) amended: MADRS, BNSS, UPSA-B total score removed from objectives & left for discussion under subsequent sections; Added tobacco use endpoint to align with the rest of the protocol; Inclusion/exclusion criteria were updated as follows: 1)subject's schizophrenia diagnosis must be supported by medical records or documented correspondence with a treating psychiatrist 2)clarified requirement for no more than 3 prior lifetime hospitalizations for the treatment of an acute psychotic episode or exacerbation of schizophrenia 3)assessment of subject's health at screening was specified to include ECG results 4)Clarified that subject eligibility must be confirmed through formal adjudication process 5) substance use disorder was amended to exclude history of significant substance abuse that could have had a permanent impact on the brain or other body systems 6) window for taking an antipsychotic equivalent to ≥ 12 mg/day of haloperidol was updated from "at screening" to "the current episode" 7)Subjects with unstable hypertension excluded. Subjects with a known cardiovascular condition, including hypertension, must be discussed with Medical Monitor (MM) before randomization. Subjects with an ECG that had a significant or potentially significant centrally read ECG alert had to be discussed with the MM. Specific blood pressure thresholds must be met for entry into the study 8) Outlined who determines clinical significance of abnormal lab values at screening; specified that the MM must approve lab retests during screening for use in determining eligibility; allowed extensions to the screening period for technical issues 9) Excluded subjects with a positive or indeterminate test for hep C, regardless of ALT or AST levels 10)Language regarding drug test results at screening was simplified. Subjects who test positive for cannabinoids at screening are excluded 11)Restrictions on prior receipt of an investigational drug product or device were expanded.
26 January 2021	Protocol Ver2.00 (16Sep2020) amended: A comparative interim analysis for unblinded sample size re-estimation was added. The purpose of the interim analysis was to assess the need for a sample size increase. Inclusion/exclusion criteria were updated as follows: 1)Based on FDA feedback, criterion regarding exclusion of subjects with a history of substantial substance use disorder that may result in significant confounding on diagnosis, presentation, and/or treatment responsiveness was revised to make the criterion more specific 2)Based on FDA feedback restrictions on prior clinical trial participation were refined to those that would meaningfully interfere with the conduct of the study 3)clarifications were made regarding medical record requirements for documenting previous course and treatment of the subject's schizophrenia illness.
13 October 2022	Protocol Ver3.00 (26Jan2021) amended: Inclusion/exclusion criteria were updated as follows: 1)clarifications made regarding medical record requirements for documenting previous course and treatment of the subject's schizophrenia illness and number of prior inpatient hospitalizations 2) range of acceptable BMI at screening was expanded to 18 to 40 kg/m2, inclusive 3) discontinuation requirement for clozapine dosed at ≤ 200 mg/day for insomnia, agitation, or anxiety was adjusted to over a 1- to 2 week period prior to randomization, as judged to be safe by the PI 4) The time requirement for prior receipt of an investigational drug product or device was reduced from 1 year to 90 days prior to signing informed consent, and the maximum lifetime participation was increased to 3 studies in psychiatric indications 5)Clarified the language regarding duration of hospitalization subsequent to last dose of study drug that would qualify as an SAE 6)Based on FDA feedback, the process for collection and recording of AEs was clarified to indicate that additional information would be collected for non-serious psychiatric AEs that led to discontinuation from the study, as well as all serious psychiatric AEs during the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Only 3 schizophrenia SAEs occurred with SEP-363856 and 1 in placebo during study drug treatment or within7days of last dose. Remaining SAEs were protocol stipulated for post-treatment hospitalization>7days after last dose. AE rates similarly impacted

Notes: