

**Clinical trial results:****A Randomised, 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	2019-000470-36
Trial protocol	BG
Global end of trial date	12 September 2023

Results information

Result version number	v2 (current)
This version publication date	31 October 2024
First version publication date	02 October 2024
Version creation reason	• Correction of full data set The sentence "p-value is adjusted onesided, calculated by Hochbergbased gatekeeping." " under the p-values (0.403 and 0.331) for CGI-S should be removed since the 2 p-values are nominal p-values, not adjusted p-values per Table 21 in 301 CSR

Trial information**Trial identification**

Sponsor protocol code	SEP361-301
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04072354
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Otsuka Pharmaceutical Development & Commercialization, Inc.
Sponsor organisation address	2440 Research Boulevard, Rockville, United States, 20850
Public contact	Clinical Transparency, Otsuka Pharmaceutical Development & Commercialization, Inc., 1 1 8446878522 , clinicaltransparency@otsuka-us.com
Scientific contact	Clinical Transparency, Otsuka Pharmaceutical Development & Commercialization, Inc., 1 8446878522, clinicaltransparency@otsuka-us.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-002589-PIP01-19
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No	Yes

1901/2006 apply to this trial?

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 September 2023
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	12 September 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to evaluate the efficacy of fixed doses of SEP-363856 (50 and 75 mg/day) compared with placebo in acutely psychotic adult subjects with schizophrenia as measured by the Positive and Negative Syndrome Scale (PANSS) total score.

Adolescent subjects were included in order to evaluate the consistency of treatment effects between adult and adolescent subjects and for the characterization of safety profile in this age group.

Protection of trial subjects:

Written informed consent, assent, or both were obtained from a legally acceptable representative (e.g., guardian) or from the subject.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 September 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 54
Country: Number of subjects enrolled	Serbia: 136
Country: Number of subjects enrolled	Ukraine: 78
Country: Number of subjects enrolled	United States: 140
Country: Number of subjects enrolled	Russian Federation: 55
Worldwide total number of subjects	463
EEA total number of subjects	54

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)	28
Adults (18-64 years)	435
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at investigational sites in the United States, Russia, Ukraine, Bulgaria, and Serbia from 17 September 2019 to 12 September 2023. Sumitomo Pharma America Inc. was the former Sponsor and conducted this study.

Pre-assignment

Screening details:

A total of 628 subjects were screened, of which 463 subjects (435 adults and 28 adolescents) were randomised to receive SEP-363856 50mg, 75 mg or placebo. Sumitomo was responsible for analysis and clinical study report (CSR) completion. Otsuka took over study after IND was transferred and is concluding activities with registry postings.

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, Data analyst, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Adults: Placebo

Arm description:

Subjects received matched SEP-363856 placebo tablet, orally, once daily up to Week 6.

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

Dosage and administration details:

Matched SEP-363856 placebo tablet, orally, once daily up to Week 6

Arm title	Adults: SEP-363856 50mg
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Arm description:

Subjects received SEP-363856 50 milligrams (mg) tablet, orally, once daily up to Week 6.

Arm type	Experimental
Investigational medicinal product name	SEP-363856 50mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

SEP-363856 50mg tablet, orally, once daily up to Week 6

Arm title	Adults: SEP-363856 75mg
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Arm description:

Subjects received SEP-363856 tablet, orally, once daily at a starting dose of 50 mg on Day 1 through Day 3 followed by dose-escalation to 75 mg from Day 4 up to Week 6.

Arm type	Experimental
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Investigational medicinal product name	SEP-363856 75mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
SEP-363856 75mg tablet, orally, once daily up to Week 6	
Arm title	Adolescents: Placebo
Arm description:	
Subjects received matched SEP-363856 placebo tablet, orally, once daily up to Week 6.	
Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Matched SEP-363856 placebo tablet, orally, once daily up to Week 6	
Arm title	Adolescents: SEP-363856 50mg
Arm description:	
Subjects received SEP-363856 50 mg tablet, orally, once daily up to Week 6.	
Arm type	Experimental
Investigational medicinal product name	SEP-363856 50mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
SEP-363856 50mg tablet, orally, once daily up to Week 6	
Arm title	Adolescents: SEP-363856 75 mg
Arm description:	
Subjects received SEP-363856 tablet, orally, once daily at a starting dose of 50 mg on Day 1 through Day 3 followed by dose-escalation to 75 mg from Day 4 up to Week 6.	
Arm type	Experimental
Investigational medicinal product name	SEP-363856 75mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
SEP-363856 75mg tablet, orally, once daily up to Week 6	

Number of subjects in period 1	Adults: Placebo	Adults: SEP-363856 50mg	Adults: SEP-363856 75mg
Started	146	144	145
Completed	119	110	118
Not completed	27	34	27
Adverse event	6	18	11
Covid-19 Related	-	1	1
Withdrawal by Subject	13	10	10
Withdrawn by subject	-	-	-
Covid-19 Related adverse event	2	-	-
Reason not specified	-	1	-
Lack of efficacy	5	4	5
Protocol deviation	1	-	-

Number of subjects in period 1	Adolescents: Placebo	Adolescents: SEP-363856 50mg	Adolescents: SEP-363856 75 mg
Started	10	9	9
Completed	10	8	8
Not completed	0	1	1
Adverse event	-	-	-
Covid-19 Related	-	-	-
Withdrawal by Subject	-	-	-
Withdrawn by subject	-	-	1
Covid-19 Related adverse event	-	-	-
Reason not specified	-	-	-
Lack of efficacy	-	1	-
Protocol deviation	-	-	-

Baseline characteristics

Reporting groups

Reporting group title	Adults: Placebo
Reporting group description:	
Subjects received matched SEP-363856 placebo tablet, orally, once daily up to Week 6.	
Reporting group title	Adults: SEP-363856 50mg
Reporting group description:	
Subjects received SEP-363856 50 milligrams (mg) tablet, orally, once daily up to Week 6.	
Reporting group title	Adults: SEP-363856 75mg
Reporting group description:	
Subjects received SEP-363856 tablet, orally, once daily at a starting dose of 50 mg on Day 1 through Day 3 followed by dose-escalation to 75 mg from Day 4 up to Week 6.	
Reporting group title	Adolescents: Placebo
Reporting group description:	
Subjects received matched SEP-363856 placebo tablet, orally, once daily up to Week 6.	
Reporting group title	Adolescents: SEP-363856 50mg
Reporting group description:	
Subjects received SEP-363856 50 mg tablet, orally, once daily up to Week 6.	
Reporting group title	Adolescents: SEP-363856 75 mg
Reporting group description:	
Subjects received SEP-363856 tablet, orally, once daily at a starting dose of 50 mg on Day 1 through Day 3 followed by dose-escalation to 75 mg from Day 4 up to Week 6.	

Reporting group values	Adults: Placebo	Adults: SEP-363856 50mg	Adults: SEP-363856 75mg
Number of subjects	146	144	145
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	35.7	36.1	37.0
standard deviation	± 10.33	± 9.38	± 10.23
Gender categorical			
Units: Subjects			
Female	73	46	59
Male	73	98	86
Ethnicity			
Units: Subjects			
Hispanic or Latino	3	5	3
Not Hispanic or Latino	143	139	142
Unknown or Not Reported	0	0	0
Race			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	2	1	0
Native Hawaiian or Other Pacific Islander	0	0	1
Black or African American	30	30	33

White	114	113	111
More than one race	0	0	0
Unknown or Not Reported	0	0	0
PANSS Total Score			
Units: Units on scale			
arithmetic mean	101.9	102.3	101.7
standard deviation	± 10.56	± 10.02	± 10.09

Reporting group values	Adolescents: Placebo	Adolescents: SEP- 363856 50mg	Adolescents: SEP- 363856 75 mg
Number of subjects	10	9	9
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	15.5	14.8	15.0
standard deviation	± 1.43	± 1.39	± 1.41
Gender categorical			
Units: Subjects			
Female	4	5	3
Male	6	4	6
Ethnicity			
Units: Subjects			
Hispanic or Latino	0	1	0
Not Hispanic or Latino	10	8	9
Unknown or Not Reported	0	0	0
Race			
Units: Subjects			
American Indian or Alaska Native	1	0	0
Asian	1	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	5	5	6
White	3	3	2
More than one race	0	0	0
Unknown or Not Reported	0	1	1
PANSS Total Score			
Units: Units on scale			
arithmetic mean	96.0	104.6	97.9
standard deviation	± 10.51	± 14.57	± 8.16

Reporting group values	Total		
Number of subjects	463		
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		

Gender categorical			
Units: Subjects			
Female	190		
Male	273		
Ethnicity			
Units: Subjects			
Hispanic or Latino	12		
Not Hispanic or Latino	451		
Unknown or Not Reported	0		
Race			
Units: Subjects			
American Indian or Alaska Native	1		
Asian	4		
Native Hawaiian or Other Pacific Islander	1		
Black or African American	109		
White	346		
More than one race	0		
Unknown or Not Reported	2		
PANSS Total Score			
Units: Units on scale			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Adults: Placebo
Reporting group description: Subjects received matched SEP-363856 placebo tablet, orally, once daily up to Week 6.	
Reporting group title	Adults: SEP-363856 50mg
Reporting group description: Subjects received SEP-363856 50 milligrams (mg) tablet, orally, once daily up to Week 6.	
Reporting group title	Adults: SEP-363856 75mg
Reporting group description: Subjects received SEP-363856 tablet, orally, once daily at a starting dose of 50 mg on Day 1 through Day 3 followed by dose-escalation to 75 mg from Day 4 up to Week 6.	
Reporting group title	Adolescents: Placebo
Reporting group description: Subjects received matched SEP-363856 placebo tablet, orally, once daily up to Week 6.	
Reporting group title	Adolescents: SEP-363856 50mg
Reporting group description: Subjects received SEP-363856 50 mg tablet, orally, once daily up to Week 6.	
Reporting group title	Adolescents: SEP-363856 75 mg
Reporting group description: Subjects received SEP-363856 tablet, orally, once daily at a starting dose of 50 mg on Day 1 through Day 3 followed by dose-escalation to 75 mg from Day 4 up to Week 6.	

Primary: Change From Baseline in PANSS Total Score at Week 6

End point title	Change From Baseline in PANSS Total Score at Week 6 ^[1]
End point description: PANSS an interview-based assessment comprised of 30 items & 3 subscales. Positive subscale assessed hallucinations, delusions & related symptoms; Negative subscale assessed emotional withdrawal, lack of motivation & similar symptoms; General Psychopathology assessed anxiety, somatic concern & disorientation. Anchored Likert scale from 1-7, where values of 2 & above indicated presence of progressively more severe symptoms was used to score each item. Individual items were then summed to determine scores for 3 subscales & a total score. PANSS total score ranges from: 30-210, higher score indicates greater severity. Negative change from baseline indicates improvement. mITT population included all randomised subjects that received atleast 1 dose of study drug & had a baseline & at least 1 post-baseline efficacy measurement in PANSS or CGI-S. This outcome measure was only assessed in Adult population. Number of subjects analysed are subjects with data available at specified timepoint.	
End point type	Primary
End point timeframe: Baseline, Week 6	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: As pre-specified in protocol the change from baseline in PANSS total score at week 6 was assessed in adult subjects only.

End point values	Adults: Placebo	Adults: SEP-363856 50mg	Adults: SEP-363856 75mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	145	142	145	
Units: score on a scale				
least squares mean (standard error)	-19.3 (± 1.55)	-16.9 (± 1.57)	-19.6 (± 1.56)	

Statistical analyses

Statistical analysis title	Change From Baseline in PANSS Total Score
Comparison groups	Adults: Placebo v Adults: SEP-363856 50mg
Number of subjects included in analysis	287
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.886 ^[2]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	Least Square (LS) Mean Difference
Point estimate	2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	6.7
Variability estimate	Standard error of the mean
Dispersion value	2.2

Notes:

[2] - P-value was analysed by MMRM method with fixed effects for treatment, visit (as a categorical variable), country, baseline PANSS total score, and treatmentbyvisit interaction. p-value is adjusted onesided, calculated by Hochbergbased gatekeeping

Statistical analysis title	Change From Baseline PANSS Total Score
Comparison groups	Adults: SEP-363856 75mg v Adults: Placebo
Number of subjects included in analysis	290
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.842 ^[3]
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.6
upper limit	4
Variability estimate	Standard error of the mean
Dispersion value	2.19

Notes:

[3] - P-value was analysed by MMRM method with fixed effects for treatment, visit (as a categorical variable), country, baseline PANSS total score, and treatmentbyvisit interaction. p-value is adjusted onesided, calculated by Hochbergbased gatekeeping.

Secondary: Change From Baseline in CGI-S Total Score at Week 6

End point title	Change From Baseline in CGI-S Total Score at Week 6 ^[4]
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End point description:

The CGI-S was a single-item clinician-rated assessment of the subject's current illness state on a 7-point scale (score range: 1-7), where a higher score was associated with greater illness severity. The mITT population included all randomised subjects that received at least 1 dose of study drug, and had a baseline and at least 1 post-baseline efficacy measurement in PANSS or CGI-S. This outcome measure was only assessed in Adult population. Number of subjects analysed are the subjects with data available at specified timepoint.

End point type	Secondary
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End point timeframe:

Baseline, Week 6

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: As pre-specified in protocol the change from baseline in CGI-S total score at week 6 was assessed in adult subjects only.

End point values	Adults: Placebo	Adults: SEP-363856 50mg	Adults: SEP-363856 75mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	145	142	145	
Units: Score				
least squares mean (standard error)	-0.90 (± 0.085)	-0.80 (± 0.086)	-1.01 (± 0.086)	

Statistical analyses

Statistical analysis title	Change From Baseline in CGI-S Score
Comparison groups	Adults: Placebo v Adults: SEP-363856 50mg
Number of subjects included in analysis	287
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.403 ^[5]
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.14
upper limit	0.34
Variability estimate	Standard error of the mean
Dispersion value	0.121

Notes:

[5] - P-value was analysed by MMRM method with fixed effects for treatment, visit (as a categorical variable), country, baseline CGI-S score, and treatmentbyvisit interaction.

Statistical analysis title	Change From Baseline in CGI-S Score
Comparison groups	Adults: Placebo v Adults: SEP-363856 75mg

Number of subjects included in analysis	290
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.331 ^[6]
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.35
upper limit	0.12
Variability estimate	Standard error of the mean
Dispersion value	0.12

Notes:

[6] - P-value was analysed by MMRM method with fixed effects for treatment, visit (as a categorical variable), country, baseline CGI-S score, and treatmentbyvisit interaction.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of study drug up to 7 days after the last dose of the study drug (up to approximately 7 weeks)

Adverse event reporting additional description:

Safety population included all randomised subjects that received at least one dose of study drug.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.0
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Reporting groups

Reporting group title	Adults: Placebo
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Reporting group description:

Subjects received matched SEP-363856 placebo tablet, orally, once daily up to Week 6.

Reporting group title	Adults: SEP-363856 50mg
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Reporting group description:

Subjects received SEP-363856 50 mg tablet, orally, once daily up to Week 6.

Reporting group title	Adults: SEP-363856 75mg
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Reporting group description:

Subjects received SEP-363856 tablet, orally, once daily at a starting dose of 50 mg on Day 1 through Day 3 followed by dose-escalation to 75 mg from Day 4 up to Week 6.

Reporting group title	Adolescents: Placebo
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Reporting group description:

Subjects received matched SEP-363856 placebo tablet, orally, once daily up to Week 6.

Reporting group title	Adolescents: SEP-363856 50mg
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Reporting group description:

Subjects received SEP-363856 50 mg tablet, orally, once daily up to Week 6.

Reporting group title	Adolescents: SEP-363856 75mg
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Reporting group description:

Subjects received SEP-363856 tablet, orally, once daily at a starting dose of 50 mg on Day 1 through Day 3 followed by dose-escalation to 75 mg from Day 4 up to Week 6.

Serious adverse events	Adults: Placebo	Adults: SEP-363856 50mg	Adults: SEP-363856 75mg
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 146 (2.74%)	11 / 144 (7.64%)	12 / 145 (8.28%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Nerve injury			
subjects affected / exposed	0 / 146 (0.00%)	0 / 144 (0.00%)	1 / 145 (0.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Tendon injury			
subjects affected / exposed	0 / 146 (0.00%)	0 / 144 (0.00%)	1 / 145 (0.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 146 (0.00%)	0 / 144 (0.00%)	1 / 145 (0.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Drug ineffective			
subjects affected / exposed	0 / 146 (0.00%)	1 / 144 (0.69%)	0 / 145 (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
Psychiatric disorders			
Schizophrenia			
subjects affected / exposed	3 / 146 (2.05%)	10 / 144 (6.94%)	12 / 145 (8.28%)
occurrences causally related to treatment / all	0 / 3	0 / 10	1 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Corona virus infection			
subjects affected / exposed	1 / 146 (0.68%)	0 / 144 (0.00%)	0 / 145 (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

Serious adverse events	Adolescents: Placebo	Adolescents: SEP- 363856 50mg	Adolescents: SEP- 363856 75mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Nerve injury			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Tendon injury			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Drug ineffective			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Schizophrenia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Corona virus infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	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	Adults: Placebo	Adults: SEP-363856 50mg	Adults: SEP-363856 75mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	41 / 146 (28.08%)	55 / 144 (38.19%)	50 / 145 (34.48%)
Investigations			
Weight decreased			
subjects affected / exposed	0 / 146 (0.00%)	0 / 144 (0.00%)	0 / 145 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			

Limb injury subjects affected / exposed occurrences (all)	0 / 146 (0.00%) 0	0 / 144 (0.00%) 0	0 / 145 (0.00%) 0
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	0 / 146 (0.00%) 0	0 / 144 (0.00%) 0	0 / 145 (0.00%) 0
Headache subjects affected / exposed occurrences (all)	9 / 146 (6.16%) 10	17 / 144 (11.81%) 18	17 / 145 (11.72%) 19
Somnolence subjects affected / exposed occurrences (all)	0 / 146 (0.00%) 0	0 / 144 (0.00%) 0	0 / 145 (0.00%) 0
General disorders and administration site conditions			
Non-cardiac chest pain subjects affected / exposed occurrences (all)	0 / 146 (0.00%) 0	0 / 144 (0.00%) 0	0 / 145 (0.00%) 0
Eye disorders			
Dry eye subjects affected / exposed occurrences (all)	0 / 146 (0.00%) 0	0 / 144 (0.00%) 0	0 / 145 (0.00%) 0
Gastrointestinal disorders			
Abdominal pain subjects affected / exposed occurrences (all)	0 / 146 (0.00%) 0	0 / 144 (0.00%) 0	0 / 145 (0.00%) 0
Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 146 (0.00%) 0	0 / 144 (0.00%) 0	0 / 145 (0.00%) 0
Constipation subjects affected / exposed occurrences (all)	0 / 146 (0.00%) 0	0 / 144 (0.00%) 0	0 / 145 (0.00%) 0
Dry mouth subjects affected / exposed occurrences (all)	0 / 146 (0.00%) 0	0 / 144 (0.00%) 0	0 / 145 (0.00%) 0
Nausea			

subjects affected / exposed occurrences (all)	11 / 146 (7.53%) 11	12 / 144 (8.33%) 13	10 / 145 (6.90%) 10
Vomiting subjects affected / exposed occurrences (all)	0 / 146 (0.00%) 0	0 / 144 (0.00%) 0	0 / 145 (0.00%) 0
Stomatitis subjects affected / exposed occurrences (all)	0 / 146 (0.00%) 0	0 / 144 (0.00%) 0	0 / 145 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all)	0 / 146 (0.00%) 0	0 / 144 (0.00%) 0	0 / 145 (0.00%) 0
Psychiatric disorders Abnormal dreams subjects affected / exposed occurrences (all)	0 / 146 (0.00%) 0	0 / 144 (0.00%) 0	0 / 145 (0.00%) 0
Agitation subjects affected / exposed occurrences (all)	7 / 146 (4.79%) 7	8 / 144 (5.56%) 12	11 / 145 (7.59%) 17
Schizophrenia subjects affected / exposed occurrences (all)	4 / 146 (2.74%) 4	16 / 144 (11.11%) 17	13 / 145 (8.97%) 15
Anxiety subjects affected / exposed occurrences (all)	7 / 146 (4.79%) 8	11 / 144 (7.64%) 13	11 / 145 (7.59%) 13
Insomnia subjects affected / exposed occurrences (all)	11 / 146 (7.53%) 15	16 / 144 (11.11%) 21	9 / 145 (6.21%) 12
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	0 / 146 (0.00%) 0	0 / 144 (0.00%) 0	0 / 145 (0.00%) 0

Non-serious adverse events	Adolescents: Placebo	Adolescents: SEP- 363856 50mg	Adolescents: SEP- 363856 75mg
Total subjects affected by non-serious adverse events subjects affected / exposed	3 / 10 (30.00%)	5 / 9 (55.56%)	6 / 9 (66.67%)

Investigations Weight decreased subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 9 (11.11%) 1
Injury, poisoning and procedural complications Limb injury subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 9 (11.11%) 1
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Somnolence subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0 1 / 10 (10.00%) 1 0 / 10 (0.00%) 0	0 / 9 (0.00%) 0 2 / 9 (22.22%) 2 0 / 9 (0.00%) 0	1 / 9 (11.11%) 1 2 / 9 (22.22%) 2 1 / 9 (11.11%) 1
General disorders and administration site conditions Non-cardiac chest pain subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 9 (11.11%) 1	0 / 9 (0.00%) 0
Eye disorders Dry eye subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Dry mouth	0 / 10 (0.00%) 0 0 / 10 (0.00%) 0 1 / 10 (10.00%) 1	0 / 9 (0.00%) 0 0 / 9 (0.00%) 0 0 / 9 (0.00%) 0	1 / 9 (11.11%) 1 1 / 9 (11.11%) 1 0 / 9 (0.00%) 0

subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 9 (11.11%) 1
Nausea subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	2 / 9 (22.22%) 2	1 / 9 (11.11%) 2
Vomiting subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0
Stomatitis subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 9 (11.11%) 1
Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0
Psychiatric disorders Abnormal dreams subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 9 (11.11%) 1
Agitation subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 9 (11.11%) 1
Schizophrenia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 9 (11.11%) 1	1 / 9 (11.11%) 1
Anxiety subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0
Insomnia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 9 (11.11%) 1	0 / 9 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 July 2019	An adolescent cohort was added based on feedback from the Food and Drug Administration (FDA).
16 September 2020	1. For the Montgomery-Asberg Depression Rating Scale (MADRS), Brief Negative Symptom Scale (BNSS), and University of California San Diego Performance-based Skills Assessment – Brief Version (UPSA-B), the specificity of “total score” was removed from the objectives and left for discussion under the endpoints and analysis sections. 2. Added tobacco use endpoint to align with the assessments collected per the Schedule of Assessments and planned analyses. 3. Inclusion/exclusion criteria were updated.
26 January 2021	1. A comparative interim analysis for unblinded sample size re-estimation was added for adult subjects only. 2. The purpose of the interim analysis was to assess the need for a sample size increase. 3. Inclusion/exclusion criteria were updated.
13 October 2022	1. Inclusion/exclusion criteria were updated. 2. Clarified the language regarding duration of hospitalization subsequent to last dose of study drug that would qualify as an SAE. 3. 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

None reported