# 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:<br>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:<br>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:<br>• Clarified that the DEQ was designed to assess subjective effects only.<br>• Clarified that subjects would remain hospitalized for the duration of the screening/washout period.<br>• Clarified inclusion criteria for acute exacerbation of psychotic symptoms and prior hospitalizations.<br>• 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).<br>• Added PANSS randomization criteria.<br>• If a subject was issued a day pass, an unscheduled urine drug screen upon returning to the site was added.<br>• Added unscheduled collection of SAS, BARS, and AIMS scales if a subject developed EPS requiring treatment.<br>• 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.<br>• Clarified that subjects were allowed 7 days to stabilize in hospital if they did not meet discharge criteria at Visit 7 or early termination.<br>• 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