



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 | <ul style="list-style-type: none">• 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 |
|-----------------------|------------|

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 |
|------------------|-------------------------|

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 |
|------------------|-------------------------|

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 | |
| 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] |
|-----------------|--|

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 |
|----------------|-----------|

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 |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 22.0 |
|--------------------|------|

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 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 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.

| 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