



Clinical trial results:

A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of SAGE-547 Injection in the Treatment of Subjects With Super-Refractory Status Epilepticus

Summary

| | |
|--------------------------|-------------------------------|
| EudraCT number | 2015-002142-31 |
| Trial protocol | DE BE SE DK ES NL FI HU AT IT |
| Global end of trial date | 11 August 2017 |

Results information

| | |
|--------------------------------|--|
| Result version number | v2 (current) |
| This version publication date | 21 September 2024 |
| First version publication date | 26 August 2018 |
| Version creation reason | <ul style="list-style-type: none">New data added to full data setChange to sponsor address. |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | 547-SSE-301 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|--------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02477618 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | IND number: 117901 |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Sage Therapeutics |
| Sponsor organisation address | 55 Cambridge Parkway, Cambridge, MA, United States, 02142 |
| Public contact | Medical Monitor, SAGE Therapeutics, 001 617-299-8380, info@sagerx.com |
| Scientific contact | Medical Monitor, SAGE Therapeutics, 001 617-299-8380, info@sagerx.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 | 11 August 2017 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 11 August 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to determine the response to a 144-hour (6-day) continuous intravenous (IV) infusion of SAGE-547 Injection (hereafter referred to as 'SAGE-547') compared to placebo administered to support the weaning of all continuous third-line agents in adult and paediatric subjects with super-refractory status epilepticus (SRSE), and for the response to endure at least 24 hours after cessation of the SAGE-547 or placebo infusion (primary response). Status epilepticus (SE) is a life-threatening condition that involves persistent or recurring seizures. SRSE is a severe form of SE that continues or recurs despite 24 hours or more of anesthetic third-line agents. Subjects with SRSE, who were admitted to the intensive care unit (ICU) and placed into a medically-induced coma, were included in the study. All subjects were critically ill due to a variety of comorbid conditions and had been in status epilepticus for a mean of 17.6 days prior to receiving study drug.

Protection of trial subjects:

This study was conducted in accordance with applicable International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines, as well as local regulations. Because most study subjects were in a state of coma, prior consent was given by a legally authorised representative. Some subjects were able to re-consent upon awakening from the coma.

Background therapy:

Third-line anti-seizure medication and medically induced coma.

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 31 July 2015 |
| 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 | Spain: 2 |
| Country: Number of subjects enrolled | United Kingdom: 2 |
| Country: Number of subjects enrolled | Austria: 1 |
| Country: Number of subjects enrolled | Denmark: 2 |
| Country: Number of subjects enrolled | Estonia: 1 |
| Country: Number of subjects enrolled | Finland: 3 |
| Country: Number of subjects enrolled | France: 3 |
| Country: Number of subjects enrolled | Italy: 9 |
| Country: Number of subjects enrolled | Canada: 4 |
| Country: Number of subjects enrolled | United States: 101 |
| Country: Number of subjects enrolled | Israel: 2 |
| Country: Number of subjects enrolled | Serbia: 2 |

| | |
|------------------------------------|-----|
| Worldwide total number of subjects | 132 |
| EEA total number of subjects | 23 |

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) | 15 |
| Adolescents (12-17 years) | 11 |
| Adults (18-64 years) | 81 |
| From 65 to 84 years | 23 |
| 85 years and over | 2 |

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at 122 investigative sites in Canada, United States, Austria, Denmark, Estonia, Finland, France, Germany, Israel, Italy, Serbia, Spain and the United Kingdom from 31 July 2015 to 11 August 2017. Note: The "Subjects Enrolled By Country" table in the "Trial Information" section reflects randomised subjects.

Pre-assignment

Screening details:

Subjects 2 years of age and older with super-refractory status epilepticus (SRSE) were eligible. The subject population was characterised by having underlying medical conditions, in addition to severe and complex SRSE, with ongoing treatment in a hospital intensive care unit (ICU), and in a medically induced coma.

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, Carer |

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | No |
| Arm title | Placebo |

Arm description:

Subjects randomised to placebo received a continuous IV infusion of matching placebo, prepared and administered identically to SAGE-547. Subjects who failed to achieve treatment success during the blinded infusion or within 24 hours of completion of the blinded infusion were potentially eligible to receive open-label SAGE-547 at a higher dose (maximum dose 150 ug/kg/hr).

| | |
|--|---------------------------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Subjects randomised to placebo received a continuous IV infusion of matching placebo, prepared and administered identically to SAGE-547. Subjects who failed to achieve treatment success during the blinded infusion or within 24 hours of completion of the blinded infusion were potentially eligible to receive open-label SAGE-547 at a higher dose (maximum dose 150 ug/kg/hr).

| | |
|------------------|----------|
| Arm title | SAGE-547 |
|------------------|----------|

Arm description:

Subjects randomized to SAGE-547 received a continuous IV infusion of SAGE-547 Injection 5 mg/mL for 144 hours. The dose regimen included a 1-hour loading infusion of 300 ug/kg/hr (0-1 hour), then 90 ug/kg/hr (2 to 120 hours), followed by a taper to 65 ug/kg/hr (121 to 128 hours), 45 ug/kg/hr (129 to 136 hours), and 25 ug/kg/hr (137 to 144 hrs). Subjects who failed to achieve treatment success during the blinded infusion or within 24 hours of completion of the blinded infusion were potentially eligible to receive open-label SAGE-547 at a higher dose (maximum dose 150 ug/kg/hr).

| | |
|--|---------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | SAGE-547 |
| Investigational medicinal product code | |
| Other name | Brexanolone |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Subjects randomized to SAGE-547 received a continuous IV infusion of SAGE-547 Injection 5 mg/mL for 144 hours. The dose regimen included a 1-hour loading infusion of 300 ug/kg/hr (0-1 hour), then 90 ug/kg/hr (2 to 120 hours), followed by a taper to 65 ug/kg/hr (121 to 128 hours), 45 ug/kg/hr (129 to 136 hours), and 25 ug/kg/hr (137 to 144 hrs). Subjects who failed to achieve treatment success during the blinded infusion or within 24 hours of completion of the blinded infusion were potentially eligible to receive open-label SAGE-547 at a higher dose (maximum dose 150 ug/kg/hr).

| Number of subjects in period 1[1] | Placebo | SAGE-547 |
|--|---------|----------|
| Started | 66 | 66 |
| Intent-to-Treat Analysis Set | 66 | 66 |
| Completed | 50 | 53 |
| Not completed | 16 | 14 |
| Adverse Event | 1 | 1 |
| Subject erroneously received SAGE-547 | 1 | - |
| Death | 11 | 11 |
| Left Study Site for Rehabilitation | - | 1 |
| Transferred Away from Study Site | 1 | - |
| Completed Visits but Discontinued Drug | 2 | 1 |
| Joined | 0 | 1 |
| Transferred in from other group/arm | - | 1 |

Notes:

[1] - The number of subjects transferring in and out of the arms in the period are not the same. It is expected the net number of transfers in and out of the arms in a period, will be zero.

Justification: The reported data are valid.

Baseline characteristics

Reporting groups^[1]

| | |
|-----------------------|---------------|
| Reporting group title | Overall Study |
|-----------------------|---------------|

| |
|--------------------------------|
| Reporting group description: - |
|--------------------------------|

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.

Justification: The reported data are valid.

| Reporting group values | Overall Study | Total | |
|------------------------|---------------|-------|--|
| Number of subjects | 132 | 132 | |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|--|---------|-----|--|
| Age continuous | | | |
| The Safety Analysis Set included all subjects who had an infusion of blinded study drug initiated. One subject randomised to placebo was erroneously given SAGE-547 and was, therefore, only included in the SAGE-547 group. | | | |
| Units: years | | | |
| arithmetic mean | 39.6 | | |
| standard deviation | ± 23.29 | - | |
| Gender categorical | | | |
| The Safety Analysis Set included all subjects who had an infusion of blinded study drug initiated. One subject randomised to placebo was erroneously given SAGE-547 and was, therefore, only included in the SAGE-547 group. | | | |
| Units: Subjects | | | |
| Female | 65 | 65 | |
| Male | 67 | 67 | |
| Race | | | |
| The Safety Analysis Set included all subjects who had an infusion of blinded study drug initiated. One subject randomised to placebo was erroneously given SAGE-547 and was, therefore, only included in the SAGE-547 group. | | | |
| Units: Subjects | | | |
| White | 92 | 92 | |
| Black | 27 | 27 | |
| Asian | 8 | 8 | |
| Other | 5 | 5 | |
| Ethnicity | | | |
| The Safety Analysis Set included all subjects who had an infusion of blinded study drug initiated. One subject randomised to placebo was erroneously given SAGE-547 and was, therefore, only included in the SAGE-547 group. | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 16 | 16 | |
| Not Hispanic or Latino | 116 | 116 | |

End points

End points reporting groups

| | |
|---|----------|
| Reporting group title | Placebo |
| Reporting group description: | |
| Subjects randomised to placebo received a continuous IV infusion of matching placebo, prepared and administered identically to SAGE-547. Subjects who failed to achieve treatment success during the blinded infusion or within 24 hours of completion of the blinded infusion were potentially eligible to receive open-label SAGE-547 at a higher dose (maximum dose 150 ug/kg/hr). | |
| Reporting group title | SAGE-547 |
| Reporting group description: | |
| Subjects randomized to SAGE-547 received a continuous IV infusion of SAGE-547 Injection 5 mg/mL for 144 hours. The dose regimen included a 1-hour loading infusion of 300 ug/kg/hr (0-1 hour), then 90 ug/kg/hr (2 to 120 hours), followed by a taper to 65 ug/kg/hr (121 to 128 hours), 45 ug/kg/hr (129 to 136 hours), and 25 ug/kg/hr (137 to 144 hrs). Subjects who failed to achieve treatment success during the blinded infusion or within 24 hours of completion of the blinded infusion were potentially eligible to receive open-label SAGE-547 at a higher dose (maximum dose 150 ug/kg/hr). | |

Primary: Percentage of Subjects Able to be Weaned Off All Third-Line Agents Prior to End of Double-Blind SAGE-547 or Placebo Infusion, and Remain Off All Third-Line Agents for ≥ 24 Hours Following the End of SAGE-547 or Placebo Infusion

| | |
|--|--|
| End point title | Percentage of Subjects Able to be Weaned Off All Third-Line Agents Prior to End of Double-Blind SAGE-547 or Placebo Infusion, and Remain Off All Third-Line Agents for ≥ 24 Hours Following the End of SAGE-547 or Placebo Infusion |
| End point description: | |
| Third-line agents (TLAs) were anaesthetic agents that were administered in order to reach a seizure or burst suppression electroencephalogram (EEG) pattern. For this study, third-line agents were defined as continuous intravenous infusions of pentobarbital/thiopental, midazolam, propofol, and ketamine at maintenance doses alone or in combination sufficient to produce a burst or seizure suppression pattern on the EEG. A responder was a subject who was able to be weaned off all third-line agents prior to the end of the SAGE-547 or placebo infusion and remain off all third-line agents for ≥ 24 hours after the end of the study drug infusion. The primary analysis was a comparison between SAGE-547 and placebo of the proportion of responders. The Intent-to-Treat Analysis Set included all subjects who had an infusion of blinded study drug initiated. | |
| End point type | Primary |
| End point timeframe: | |
| 7 days | |

| End point values | Placebo | SAGE-547 | | |
|-------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 66 | 66 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 42.4 | 43.9 | | |

Statistical analyses

| | |
|---|----------------------------------|
| Statistical analysis title | Weaning of all third-line agents |
| Comparison groups | Placebo v SAGE-547 |
| Number of subjects included in analysis | 132 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.878 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.056 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.527 |
| upper limit | 2.118 |

Secondary: Time Between the Primary Outcome Response and the Re-institution of Any Third-line Agent for Seizure or Burst Suppression

| | |
|--|---|
| End point title | Time Between the Primary Outcome Response and the Re-institution of Any Third-line Agent for Seizure or Burst Suppression |
| End point description: | |
| Third-line agents were anaesthetic agents that were administered in order to reach a seizure or burst suppression EEG pattern. For this study, third-line agents were defined as continuous intravenous infusions of pentobarbital/thiopental, midazolam, propofol, and ketamine at maintenance doses alone or in combination sufficient to produce a burst or seizure suppression pattern on the EEG. A responder was a subject who was able to be weaned off all third-line agents prior to the end of the SAGE-547 or placebo infusion and remain off all third-line agents for ≥ 24 hours after the end of the study drug infusion. The primary analysis was a comparison between SAGE-547 and placebo of the proportion of responders. The Intent-to-Treat Analysis Set included all subjects who had an infusion of blinded study drug initiated. Here, overall number of subjects analysed (n) indicates subjects analysed for this outcome measure. | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 21 days | |

| | | | | |
|-------------------------------|------------------------|------------------------|--|--|
| End point values | Placebo | SAGE-547 | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 28 | 29 | | |
| Units: days | | | | |
| median (full range (min-max)) | 13.500 (0.06 to 18.00) | 14.000 (0.18 to 16.00) | | |

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | Time to event: Re-institution of any TLA |
| Comparison groups | Placebo v SAGE-547 |

| | |
|---|-------------------|
| Number of subjects included in analysis | 57 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.636 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.747 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.222 |
| upper limit | 2.507 |

Secondary: Percentage of Subjects Able to be Weaned Off All Third-line Agents Before the End of the First SAGE-547 or Placebo Infusion

| | |
|--|---|
| End point title | Percentage of Subjects Able to be Weaned Off All Third-line Agents Before the End of the First SAGE-547 or Placebo Infusion |
| End point description: Third-line agents were anaesthetic agents that were administered in order to reach a seizure or burst suppression EEG pattern. For this study, third-line agents were defined as continuous intravenous infusions of pentobarbital/thiopental, midazolam, propofol, and ketamine at maintenance doses alone or in combination sufficient to produce a burst or seizure suppression pattern on the EEG. The Intent-to-Treat Analysis Set included all subjects who had an infusion of blinded study drug initiated. | |
| End point type | Secondary |
| End point timeframe: Day 6 | |

| End point values | Placebo | SAGE-547 | | |
|-------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 66 | 66 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 68.2 | 57.6 | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Subjects able to be weaned off all TLA: Day 6 |
| Comparison groups | Placebo v SAGE-547 |
| Number of subjects included in analysis | 132 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.199 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.623 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.303 |
| upper limit | 1.282 |

Secondary: Time Between the Secondary Outcome Measure Response and the Re-institution of Any Third-line Agent for Seizure or Burst Suppression

| | |
|-----------------|---|
| End point title | Time Between the Secondary Outcome Measure Response and the Re-institution of Any Third-line Agent for Seizure or Burst Suppression |
|-----------------|---|

End point description:

Third-line agents were anaesthetic agents that were administered in order to reach a seizure or burst suppression EEG pattern. For this study, third-line agents were defined as continuous intravenous infusions of pentobarbital/thiopental, midazolam, propofol, and ketamine at maintenance doses alone or in combination sufficient to produce a burst or seizure suppression pattern on the EEG. The Intent-to-Treat Analysis Set included all subjects who had an infusion of blinded study drug initiated. Here, overall number of subjects analysed (n) indicates subjects analysed for this outcome measure.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 21 days

| End point values | Placebo | SAGE-547 | | |
|-------------------------------|-----------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 45 | 38 | | |
| Units: days | | | | |
| median (full range (min-max)) | 7.000 (0.00 to 20.00) | 15.000 (0.00 to 19.00) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Time to event: Re-institution of any TLA |
| Comparison groups | Placebo v SAGE-547 |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.328 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.683 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.318 |
| upper limit | 1.466 |

Secondary: Change in Clinical Global Impression Scale (CGI)

| | |
|-----------------|--|
| End point title | Change in Clinical Global Impression Scale (CGI) |
|-----------------|--|

End point description:

The CGI scale was used to integrate several sources of information into a single rating of a subject's condition. The CGI was rated on a 7-point scale, from a minimum of 0 to a maximum of 7, where 0 = Not assessed; 1 = Normal, not at all ill; 2 = Borderline physically ill; 3 = Mildly ill; 4 = Moderately ill; 5 = Markedly ill; 6 = Severely ill; 7 = Among the most extremely ill subjects. A negative change from baseline indicates improvement. A positive change from baseline indicates worsening. The Intent-to-Treat Analysis Set included all subjects who had an infusion of blinded study drug initiated. Here, number of subjects analysed (n) indicates subjects with available data at each time point. The study visits followed by "R" indicate the Open-label Treatment Period.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 21 days

| End point values | Placebo | SAGE-547 | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 66 | 66 | | |
| Units: units on scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n=66, 65) | 6.0 (± 0.89) | 5.9 (± 1.31) | | |
| Visit 12 (n=33, 32) | -1.0 (± 1.42) | -0.6 (± 1.91) | | |
| Visit 12R (n=18, 20) | -0.7 (± 1.36) | -0.5 (± 1.19) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Days After the End of the First Study Drug Infusion Without Status Epilepticus, Up to Visit 12

| | |
|-----------------|--|
| End point title | Number of Days After the End of the First Study Drug Infusion Without Status Epilepticus, Up to Visit 12 |
|-----------------|--|

End point description:

The Intent-to-Treat Analysis Set included all subjects who had an infusion of blinded study drug initiated. Here, number of subjects analysed (n) indicates subjects with available data at each time point for this outcome measure. The study visits followed by "R" indicate the Open-label Treatment Period.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 21 days

| End point values | Placebo | SAGE-547 | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 66 | 66 | | |
| Units: days | | | | |
| arithmetic mean (standard deviation) | | | | |
| Visit 12 (n=41,40) | 10.05 (± 6.738) | 11.15 (± 6.058) | | |
| Visit 12R (n=25,26) | 11.08 (± 6.557) | 9.23 (± 6.345) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Number of days: Without Status Epilepticus |
| Comparison groups | Placebo v SAGE-547 |
| Number of subjects included in analysis | 132 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.339 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.583 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.193 |
| upper limit | 1.763 |

Secondary: Number of Days After the End of the First Study Drug Infusion Without Seizures (Convulsive and Non-convulsive), up to Visit 12

| | |
|---|--|
| End point title | Number of Days After the End of the First Study Drug Infusion Without Seizures (Convulsive and Non-convulsive), up to Visit 12 |
| End point description: | |
| The Intent-to-Treat Analysis Set included all subjects who had an infusion of blinded study drug initiated. Here, number of subjects analysed (n) indicates subjects with available data at each time point. The study visits followed by "R" indicate the Open-label Treatment Period. | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 21 days | |

| End point values | Placebo | SAGE-547 | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 66 | 66 | | |
| Units: days | | | | |
| arithmetic mean (standard deviation) | | | | |
| Visit 12 (n=41,40) | 8.22 (± 7.289) | 7.50 (± 6.626) | | |
| Visit 12R (n=25,26) | 7.52 (± 7.054) | 6.08 (± 5.932) | | |

Statistical analyses

| Statistical analysis title | Number of days without seizures |
|---|---------------------------------|
| Comparison groups | Placebo v SAGE-547 |
| Number of subjects included in analysis | 132 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.817 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.086 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.539 |
| upper limit | 2.189 |

Secondary: Number of Separate Episodes of Status Epilepticus Up to Visit 12

| | |
|------------------------|--|
| End point title | Number of Separate Episodes of Status Epilepticus Up to Visit 12 |
| End point description: | The Intent-to-Treat Analysis Set included all subjects who had an infusion of blinded study drug initiated. Here, number of subjects analysed (n) indicates subjects with available data at each time point for this outcome measure. The study visits followed by "R" indicate the Open-label Treatment Period. |
| End point type | Secondary |
| End point timeframe: | Up to 21 days |

| End point values | Placebo | SAGE-547 | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 66 | 66 | | |
| Units: episodes | | | | |
| arithmetic mean (standard deviation) | | | | |
| Visit 12 (n=9,5) | 1.3 (± 0.50) | 1.4 (± 0.55) | | |
| Visit 12R (n=5,8) | 2.2 (± 2.17) | 1.0 (± 0.00) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Number of separate episodes of status epilepticus |
| Comparison groups | Placebo v SAGE-547 |
| Number of subjects included in analysis | 132 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.567 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.9 |
| upper limit | 0.5 |

Secondary: Number of Subjects With a New Diagnosis of Epilepsy After Visit 11

| | |
|--|--|
| End point title | Number of Subjects With a New Diagnosis of Epilepsy After Visit 11 |
| End point description: The Intent-to-Treat Analysis Set included all subjects who had an infusion of blinded study drug initiated. Here, number of subjects analysed (n) indicates subjects with available data at each time point for this outcome measure. The study visits followed by "R" indicate the Open-label Treatment Period. | |
| End point type | Secondary |
| End point timeframe: Up to 21 days | |

| | | | | |
|-----------------------------|-----------------|-----------------|--|--|
| End point values | Placebo | SAGE-547 | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 66 | 66 | | |
| Units: subjects | | | | |
| Visit 12 (n=34,34) | 0 | 5 | | |
| Visit 12R (n=20,23) | 5 | 3 | | |

Statistical analyses

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 27 days

Adverse event reporting additional description:

The Safety Analysis Set included all subjects who had an infusion of blinded study drug initiated. The subject population was characterised by having underlying medical conditions, in addition to severe and complex SRSE, with ongoing treatment in a hospital intensive care unit (ICU), and in a medically induced coma.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 19.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------|
| Reporting group title | SAGE-547 |
|-----------------------|----------|

Reporting group description:

Subjects randomized to SAGE-547 received a continuous IV infusion of SAGE-547 Injection 5 mg/mL for 144 hours. The dose regimen included a 1-hour loading infusion of 300 ug/kg/hr (0-1 hour), then 90 ug/kg/hr (2 to 120 hours), followed by a taper to 65 ug/kg/hr (121 to 128 hours), 45 ug/kg/hr (129 to 136 hours), and 25 ug/kg/hr (137 to 144 hrs). Subjects who failed to achieve treatment success during the blinded infusion or within 24 hours of completion of the blinded infusion were potentially eligible to receive open-label SAGE-547 at a higher dose (maximum dose 150 ug/kg/hr).

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Subjects randomised to placebo received a continuous IV infusion of matching placebo, prepared and administered identically to SAGE-547. Subjects who failed to achieve treatment success during the blinded infusion or within 24 hours of completion of the blinded infusion were potentially eligible to receive open-label SAGE-547 at a higher dose (maximum dose 150 ug/kg/hr).

| Serious adverse events | SAGE-547 | Placebo | |
|---|------------------|------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 27 / 67 (40.30%) | 22 / 65 (33.85%) | |
| number of deaths (all causes) | 17 | 12 | |
| number of deaths resulting from adverse events | | | |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 2 / 67 (2.99%) | 1 / 65 (1.54%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Neurogenic shock | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 65 (1.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |

| | | | |
|--|------------------|-----------------|--|
| Surgical and medical procedures | | | |
| Withdrawal of life support | | | |
| subjects affected / exposed | 11 / 67 (16.42%) | 7 / 65 (10.77%) | |
| occurrences causally related to treatment / all | 0 / 11 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Hypothermia | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 65 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related thrombosis | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 65 (1.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperthermia | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 65 (1.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 65 (1.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Respiratory failure | | | |
| subjects affected / exposed | 2 / 67 (2.99%) | 1 / 65 (1.54%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 65 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Hypoxia | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 65 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Obstructive airways disorder | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 65 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 65 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 65 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 65 (1.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary oedema | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 65 (1.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory arrest | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 65 (1.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Psychiatric disorders | | | |
| Delirium | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 65 (1.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Product issues | | | |

| | | | |
|---|----------------|----------------|--|
| Device dislocation | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 65 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Transaminases increased | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 1 / 65 (1.54%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 65 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 65 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nuclear magnetic resonance imaging brain abnormal | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 65 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Liver function test abnormal | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 65 (1.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Subdural haematoma | | | |
| subjects affected / exposed | 2 / 67 (2.99%) | 1 / 65 (1.54%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Brain herniation | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 67 (1.49%) | 3 / 65 (4.62%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 1 / 2 | |
| Nerve injury | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 65 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Congenital, familial and genetic disorders | | | |
| Mitochondrial DNA mutation | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 65 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardiac disorders | | | |
| Cardiac arrest | | | |
| subjects affected / exposed | 5 / 67 (7.46%) | 4 / 65 (6.15%) | |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 5 | 0 / 2 | |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 1 / 65 (1.54%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Pulseless electrical activity | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 1 / 65 (1.54%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Atrial flutter | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 65 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bradycardia | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 65 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Bundle branch block | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 65 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Torsade de pointes | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 65 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Ventricular fibrillation | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 65 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Nodal rhythm | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 65 (1.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular tachycardia | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 65 (1.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Brain oedema | | | |
| subjects affected / exposed | 2 / 67 (2.99%) | 1 / 65 (1.54%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Status epilepticus | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 2 / 65 (3.08%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |
| Cerebral atrophy | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 65 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral infarction | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 65 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Posterior reversible encephalopathy syndrome | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 65 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral ischaemia | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 65 (1.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 65 (1.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Mydriasis | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 65 (1.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pupil fixed | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 65 (1.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Intestinal ischaemia | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 1 / 65 (1.54%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal compartment syndrome | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 65 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Ileus | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 65 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Melaena | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 65 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 65 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intra-abdominal haemorrhage | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 65 (1.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholestasis | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 65 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cirrhosis alcoholic | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 65 (1.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic failure | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 65 (1.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 65 (1.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|---|----------------|----------------|--|
| Drug reaction with eosinophilia and systemic symptoms | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 65 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angioedema | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 65 (1.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 65 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| Diabetes insipidus | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 2 / 65 (3.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Septic shock | | | |
| subjects affected / exposed | 3 / 67 (4.48%) | 2 / 65 (3.08%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 3 / 65 (4.62%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 2 / 65 (3.08%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia staphylococcal | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 65 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Serratia sepsis | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 65 (1.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subdural empyema | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 65 (1.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 65 (1.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Metabolic acidosis | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 1 / 65 (1.54%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 65 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Propofol infusion syndrome | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 65 (1.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |

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

| Non-serious adverse events | SAGE-547 | Placebo | |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 60 / 67 (89.55%) | 58 / 65 (89.23%) | |
| Investigations | | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 5 / 67 (7.46%) | 6 / 65 (9.23%) | |
| occurrences (all) | 5 | 6 | |
| Lipase increased | | | |
| subjects affected / exposed | 5 / 67 (7.46%) | 6 / 65 (9.23%) | |
| occurrences (all) | 5 | 6 | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 4 / 67 (5.97%) | 5 / 65 (7.69%) | |
| occurrences (all) | 4 | 5 | |
| Blood potassium decreased | | | |
| subjects affected / exposed | 4 / 67 (5.97%) | 1 / 65 (1.54%) | |
| occurrences (all) | 4 | 1 | |
| White blood cell count increased | | | |
| subjects affected / exposed | 4 / 67 (5.97%) | 0 / 65 (0.00%) | |
| occurrences (all) | 6 | 0 | |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 3 / 67 (4.48%) | 4 / 65 (6.15%) | |
| occurrences (all) | 6 | 5 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 8 / 67 (11.94%) | 6 / 65 (9.23%) | |
| occurrences (all) | 8 | 6 | |
| Hypotension | | | |
| subjects affected / exposed | 6 / 67 (8.96%) | 10 / 65 (15.38%) | |
| occurrences (all) | 7 | 10 | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 3 / 67 (4.48%) | 4 / 65 (6.15%) | |
| occurrences (all) | 5 | 4 | |
| Cardiac disorders | | | |
| Tachycardia | | | |
| subjects affected / exposed | 8 / 67 (11.94%) | 4 / 65 (6.15%) | |
| occurrences (all) | 8 | 4 | |
| Atrial fibrillation | | | |

| | | | |
|--|------------------------|------------------------|--|
| subjects affected / exposed occurrences (all) | 5 / 67 (7.46%) 10 | 2 / 65 (3.08%) 2 | |
| Sinus tachycardia subjects affected / exposed occurrences (all) | 4 / 67 (5.97%) 6 | 0 / 65 (0.00%) 0 | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 12 / 67 (17.91%) 12 | 7 / 65 (10.77%) 9 | |
| Leukocytosis subjects affected / exposed occurrences (all) | 4 / 67 (5.97%) 6 | 3 / 65 (4.62%) 3 | |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 3 / 67 (4.48%) 3 | 7 / 65 (10.77%) 8 | |
| General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all) | 19 / 67 (28.36%) 31 | 21 / 65 (32.31%) 34 | |
| Hyperthermia subjects affected / exposed occurrences (all) | 5 / 67 (7.46%) 5 | 1 / 65 (1.54%) 1 | |
| Peripheral swelling subjects affected / exposed occurrences (all) | 4 / 67 (5.97%) 5 | 0 / 65 (0.00%) 0 | |
| Oedema subjects affected / exposed occurrences (all) | 3 / 67 (4.48%) 3 | 4 / 65 (6.15%) 4 | |
| Hypothermia subjects affected / exposed occurrences (all) | 1 / 67 (1.49%) 1 | 4 / 65 (6.15%) 4 | |
| Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) | 12 / 67 (17.91%) 12 | 7 / 65 (10.77%) 7 | |
| Constipation | | | |

| | | | |
|---|------------------------|-----------------------|--|
| subjects affected / exposed occurrences (all) | 10 / 67 (14.93%) 12 | 8 / 65 (12.31%) 11 | |
| Vomiting subjects affected / exposed occurrences (all) | 5 / 67 (7.46%) 5 | 2 / 65 (3.08%) 2 | |
| Abdominal distension subjects affected / exposed occurrences (all) | 4 / 67 (5.97%) 4 | 0 / 65 (0.00%) 0 | |
| Respiratory, thoracic and mediastinal disorders Pleural effusion subjects affected / exposed occurrences (all) | 14 / 67 (20.90%) 14 | 8 / 65 (12.31%) 9 | |
| Atelectasis subjects affected / exposed occurrences (all) | 5 / 67 (7.46%) 6 | 4 / 65 (6.15%) 4 | |
| Pulmonary oedema subjects affected / exposed occurrences (all) | 3 / 67 (4.48%) 3 | 4 / 65 (6.15%) 4 | |
| Skin and subcutaneous tissue disorders Decubitus ulcer subjects affected / exposed occurrences (all) | 5 / 67 (7.46%) 5 | 8 / 65 (12.31%) 10 | |
| Erythema subjects affected / exposed occurrences (all) | 4 / 67 (5.97%) 4 | 2 / 65 (3.08%) 8 | |
| Rash subjects affected / exposed occurrences (all) | 4 / 67 (5.97%) 4 | 2 / 65 (3.08%) 2 | |
| Psychiatric disorders Agitation subjects affected / exposed occurrences (all) | 5 / 67 (7.46%) 5 | 4 / 65 (6.15%) 4 | |
| Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all) | 4 / 67 (5.97%) 4 | 1 / 65 (1.54%) 1 | |

| | | | |
|--|------------------------|------------------------|--|
| Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all) | 13 / 67 (19.40%) 14 | 14 / 65 (21.54%) 14 | |
| Pneumonia subjects affected / exposed occurrences (all) | 13 / 67 (19.40%) 15 | 11 / 65 (16.92%) 12 | |
| Fungal infection subjects affected / exposed occurrences (all) | 4 / 67 (5.97%) 4 | 1 / 65 (1.54%) 1 | |
| Sepsis subjects affected / exposed occurrences (all) | 3 / 67 (4.48%) 3 | 4 / 65 (6.15%) 4 | |
| Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all) | 10 / 67 (14.93%) 10 | 11 / 65 (16.92%) 14 | |
| Hypophosphataemia subjects affected / exposed occurrences (all) | 8 / 67 (11.94%) 8 | 6 / 65 (9.23%) 6 | |
| Metabolic acidosis subjects affected / exposed occurrences (all) | 8 / 67 (11.94%) 8 | 2 / 65 (3.08%) 2 | |
| Hypernatraemia subjects affected / exposed occurrences (all) | 6 / 67 (8.96%) 6 | 6 / 65 (9.23%) 6 | |
| Hyponatraemia subjects affected / exposed occurrences (all) | 5 / 67 (7.46%) 5 | 4 / 65 (6.15%) 4 | |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 5 / 67 (7.46%) 5 | 1 / 65 (1.54%) 1 | |
| Hyperammonaemia subjects affected / exposed occurrences (all) | 5 / 67 (7.46%) 5 | 0 / 65 (0.00%) 0 | |
| Fluid overload | | | |

| | | | |
|-----------------------------|----------------|-----------------|--|
| subjects affected / exposed | 4 / 67 (5.97%) | 2 / 65 (3.08%) | |
| occurrences (all) | 4 | 2 | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 3 / 67 (4.48%) | 7 / 65 (10.77%) | |
| occurrences (all) | 3 | 7 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 27 May 2015 | <ul style="list-style-type: none">• Added Europe to the list of regions with study sites• Added the requirement for maintenance of burst suppression for the first 12 hours of the study drug infusion• Increased the sample size from 126 to 140 (with the intent of obtaining 126 evaluable subjects)• Added that all subjects who failed to complete their randomised treatment infusion or did not have at least one attempt to wean off all TLAs during study treatment were considered "failures" for the primary endpoint• Established the Clinical Standardization Guidelines and Team to assist sites and create consistency with weaning practices across study sites• Added qualifying wean (QW) guidance• Added the collection of Health Economics and Outcome data for subjects who were discharged from intensive care unit (ICU) prior to completion of Visit 12/12R• Added the Status Epilepticus Severity Score assessment during Visit 1 |
| 28 October 2015 | <ul style="list-style-type: none">• Removed paediatric subjects |
| 17 November 2015 | <ul style="list-style-type: none">• Increased the number of study sites to up to 180 sites• Revised the list of accepted TLAs to include thiopental 3 mg/kg/h• Extended the QW EEG for the blinded study drug infusion to cover the 24 hours after the end of TLAs in order to confirm that the QW was a success• Added the consent EEG and blinded infusion EEG to the EEG records to be read centrally to capture the depth of burst suppression prior to QW and during the first 12 hours of the blinded infusion |
| 22 April 2016 | Never implemented. |
| 12 August 2016 | <ul style="list-style-type: none">• Added Israel to the list of regions with study sites• Refined exclusion criteria, to exclude subjects who had been treated or randomised in this or any other SAGE-547 study with the intent of allowing subjects previously screened who subsequently met entry criteria• Provided additional guidance for TLA weaning• Extended the time frame from QW failure to when blinded infusion began to 8 hours• Removed an exclusion criterion 5 sub-bullet due to variations of interpretations of a "Do Not Resuscitate" order across sites• Removed the requirement for subjects to be in EEG burst suppression in the 24 hours prior to the QW |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported