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	v1
This version publication date	26 August 2018
First version publication date	26 August 2018

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	215 First Street, 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: One subject randomised to placebo was erroneously given SAGE-547 and was, therefore, included in the SAGE-547 group.

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: One subject randomised to placebo was erroneously given SAGE-547 and was, therefore, included in the SAGE-547 group.

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 standard deviation	 39.6 ± 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

No statistical analyses for this end point

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	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).

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

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

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

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

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

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

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

Ileus			
subjects affected / exposed	0 / 65 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	0 / 65 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 65 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal haemorrhage			
subjects affected / exposed	1 / 65 (1.54%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	0 / 65 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cirrhosis alcoholic			
subjects affected / exposed	1 / 65 (1.54%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 65 (1.54%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	1 / 65 (1.54%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
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	0 / 65 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angioedema			
subjects affected / exposed	1 / 65 (1.54%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 65 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Diabetes insipidus			
subjects affected / exposed	2 / 65 (3.08%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Septic shock			
subjects affected / exposed	2 / 65 (3.08%)	3 / 67 (4.48%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 65 (4.62%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sepsis			
subjects affected / exposed	2 / 65 (3.08%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia staphylococcal			

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

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

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 May 2015	• 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	• Removed paediatric subjects
17 November 2015	• 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	• 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