

**NIHR Innovation Observatory
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SAGE-547 for super-refractory status epilepticus

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Status epilepticus is a single epileptic seizure lasting more than five minutes or two or more seizures within a five-minute period without the person returning to baseline between them. Status epilepticus is categorized as early, established, refractory and super-refractory. Patients with refractory status epilepticus (RSE) have failed first and second line agents (typically benzodiazepines and other antiepileptic medication) and are generally treated with anaesthetic therapy. Super-refractory status epilepticus (SRSE) is defined as status epilepticus that continues or recurs 24 hours or more after the onset of anaesthetic therapy, including those cases where status epilepticus recurs on the reduction or withdrawal of anaesthesia.

SAGE-547 is a novel investigational drug which is being studied in clinical development as an adjunct therapy for the treatment of super-refractory status epilepticus. The treatment is being considered in trials for the patients aged two years and older.

This briefing is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

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TARGET GROUP

- Patients with super-refractory status epilepticus; aged two years or older; receiving third line agents/anaesthetics.

TECHNOLOGY

DESCRIPTION

SAGE-547; a proprietary formulation of Allopregnanolone, an endogenous neuroactive steroid, is under development for the treatment of super-refractory status epilepticus (SRSE). SAGE-547 is an allosteric modulator of both synaptic and extra-synaptic GABAA receptors. SAGE-547 is intended for dilution and subsequent continuous IV administration which, in the case of SRSE, would occur in an intensive care unit setting for up to two 6-day treatments (total 12 days).

In the phase III clinical trial in super-refractory status epilepticus (SRSE), patients aged 2 years or older are randomized to receive SAGE-547 versus placebo for a 6-day continuous infusion and non-responders are eligible for a 6 six day continuous infusion of open label high dose SAGE-547 infusion. SAGE-547 is currently also in phase III trials for both Severe and Moderate Postpartum Depression. SAGE-547 does not currently have Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

If licensed, SAGE-547 will offer a novel treatment option for SRSE patients in a population with limited effective treatment options.

DEVELOPER

Sage Therapeutics

AVAILABILITY, LAUNCH or MARKETING

In April 2014, the FDA granted brexanolone Orphan Drug designation for the treatment of status epilepticus; including SRSE.¹

In July 2014, the FDA granted Fast Track designation for the treatment of SRSE.¹

PATIENT GROUP

BACKGROUND

Status epilepticus (SE) is a rare, serious and acute life-threatening condition in which abnormal and excessive activity in the brain is unremitting. SE is an acute neurological medical emergency associated, in its more severe forms, with significant mortality and morbidity. SE is defined as a seizure lasting more than 5 min or recurrent seizure activity without recovery (returning to baseline) between seizures.²⁻⁴ Primarily treated in the Intensive Care Unit (ICU), refractory SE (RSE) is defined as seizures that continue despite the administration of an initial first line agent (typically a benzodiazepine), followed by a second-line intravenous (IV) anti-epileptic drug (AED), such as phenytoin, fosphenytoin, levetiracetam, or valproate.⁴ SE that persists for 24 h or more following onset of therapy with third-line agents/anesthetics (e.g. propofol, midazolam, thiopental,) or after the reduction or withdrawal of third-line agents is defined as super-refractory SE (SRSE.)⁵

Risk factors for SRSE are strongly linked to its aetiology, and there is significant variation in these when analysed by age group. Infection with fever not involving the central nervous system (CNS) as the major aetiology of SE in children, followed by remote CNS insult and low anticonvulsant drug levels; meanwhile, other major aetiologies were observed in adults: anoxia, hypoxia, low antiepileptic drug levels, alcohol, trauma, CNS infections, other infectious diseases, genetic disorders, low anticonvulsant drugs, remote symptomatic epilepsy and stroke.^{3, 6-9}

CLINICAL NEED and BURDEN OF DISEASE

Status epilepticus, RSE, and SRSE are rare conditions and the incidence of each of these conditions is estimated to be approximately 4-6/10,000 in the European Union. In reports specific to countries in the European Union the annual incidence of status epilepticus ranges from 1.3 to 2.7 per 10,000^{3,4,5} Prevalence estimates for SRSE based on the published literature differ country-to-country likely as a result of differences in the prevalence or rate of occurrence of the underlying conditions and disorders that cause SRSE; challenges in making an accurate diagnosis of SRSE, particularly in a patient population with multiple complications; limitations and variations in the diagnosis coding for these conditions; the small size of the populations studied in the literature; and differences and limitations in the analytical plans underlying the various published studies.

Causes of death in patients with SRSE are heterogeneous, resulting from neurological complications directly related to the underlying aetiology and the continuous seizure activity, complications of comorbid medical conditions often related to prolonged ICU admissions, or adverse effects of the current treatments.

In 2015 to 16, there were 41647, 4036 and 44181 hospital admissions for epilepsy (ICD-10 G40), status epilepticus (ICD-10 G41) and convulsions (ICD-10 R56), respectively. In England resulting in 55208, 6492 and 55932 finished consultant episodes.¹⁰

In 2014, there were 75 deaths from status epilepticus in England and Wales.¹¹ It is estimated that 15% of all the cases with status epilepticus admitted to hospital will become super-refractory.¹⁰

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE clinical guidelines. Epilepsies: diagnosis and management (CG137). January 2012.
- NICE quality standard. Epilepsy in adults (QS26). February 2013.
- NICE quality standard. Epilepsy in children and young people (QS27). February 2013.
- NICE interventional procedure guidance. Deep brain stimulation for refractory epilepsy (IPG416). January 2012.
- NICE interventional procedure guidance. Vagus nerve stimulation for refractory epilepsy in children (IPG50). March 2004.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Neurosciences: Specialised Neurology (Adult). ED04/S/a.
- NHS England. Clinical Commissioning Policy: Deep Brain Stimulation for Refractory Epilepsy. D03/P/c.
- NHS England. Clinical Commissioning Policy: Vagal Nerve Stimulation for Epilepsy. D04/P/r
- NHS England. 2013/14 NHS Standard Contract for Paediatric Neurosciences: Neurology. E09/S/b.
- NHS England. 2013/14 NHS Standard Contract for Children's Epilepsy Surgery Service (CESS). E09/S/e.

OTHER GUIDANCE

No guidance is currently available.

CURRENT TREATMENT OPTIONS

There is no currently regulatory-approved treatment throughout the EU specifically for SRSE, or for RSE. Since patients with RSE have failed to respond to first-line benzodiazepines (typically lorazepam, diazepam or midazolam) and second-line antiepileptic drug (AED) therapies (typically phenytoin/fosphenytoin, phenobarbital, levetiracetam or valproate), anaesthetics used to place the patient in a medically induced coma are the mainstay of treatment. It is conventional to continue the administration of second-line AEDs and continually attempt to optimize the AED regimen while the anaesthetics are administered. Treatment approaches for SRSE consist of diagnosis and treatment of the triggering and comorbid medical conditions, adding and changing AEDs, and repeated attempts at weaning from intravenous (IV) anaesthetic agents.

Convulsive status epilepticus may be treated with a buccal midazolam or rectal diazepam for use in the community for children, young people and adults who have had a previous episode of prolonged or serial convulsive seizures.¹²

Buccal midazolam can be administered as first-line treatment in children, young people and adults with prolonged or repeated seizures in the community. Rectal diazepam can be used if preferred or if buccal midazolam is not available. If intravenous access is already established and resuscitation facilities are available, intravenous lorazepam should be administered.¹²

NICE guideline for epilepsies recommends the following treatments for convulsive status epilepticus in adults¹²:

- 1st stage (0–10 minutes): secure airway and resuscitate; administer oxygen; assess cardiorespiratory function; establish intravenous access.
- 2nd stage (0–30 minutes): Institute regular monitoring; consider the possibility of non-epileptic status; emergency AED therapy; emergency investigations; administer glucose (50 ml of 50% solution) and/or intravenous thiamine (250 mg) as high potency intravenous Pabrinex if any suggestion of alcohol abuse or impaired nutrition; treat acidosis if severe.
- 3rd stage (0–60 minutes): establish aetiology; alert anaesthetist and ITU; identify and treat medical complications; pressor therapy when appropriate.
- 4th stage (30–90 minutes): transfer to intensive care; establish intensive care and EEG monitoring; initiate intracranial pressure monitoring where appropriate; initiate long-term, maintenance AED therapy.

And in children and young people:

- 1st stage (0 minute): seizure starts; check ABC, high flow O2 if available; check blood glucose.
- 2nd stage (5 minutes): Midazolam 0.5 mg/kg buccally; or Lorazepam 0.1 mg/kg if intravenous access established.
- 3rd stage (15 minutes): Lorazepam 0.1 mg/kg intravenously.
- 4th stage (25 minutes): Phenytoin 20 mg/kg by intravenous infusion over 20 mins; or (if on regular phenytoin) Phenobarbital 20 mg/kg intravenously over 5 mins.
- 5th stage (45 minutes): sodium 4 mg/kg intravenously, and Transfer to paediatric intensive care unit.

EFFICACY and SAFETY

Trial	SAGE-547, NCT02477618; 2 Years and older; SAGE 547 vs Placebo; phase III	SAGE-547; NCT02052739; 2 years and older; phase I/II
Sponsor	Sage Therapeutics	Sage Therapeutics
Status	Ongoing	Completed
Source of information	Trial registry ¹³ ; pharma project ¹⁴	Trial registry ¹⁵ ; pharma project ¹⁶
Location	EU (incl UK), ISRAEL, USA and Canada	USA

Design	Randomized, double-blind, placebo-controlled	Open label
Participants	n=up to 126 evaluable; aged 2 years and older; failed to respond to the administration of at least one first-line agent; failed to respond to at least one second-line agent; not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; or who have previously failed zero, one or more wean attempts from third-line agents and are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst or seizure suppression pattern; or who have previously failed one or more wean attempts from third-line agents and are now either not on a continuous intravenous infusion of at least one third-line agent or are on a continuous intravenous infusion of one or more third-line agent but not in an EEG burst or seizure suppression pattern	n=25; aged 2 years and older; Patients with an EEG-confirmed SRSE diagnosis under concomitant therapy with continuous IV AED (third line agent) for > or = 24 hours.
Schedule	Patients are randomized 1;1 to receive either SAGE-547 or placebo in addition to standard-of-care third-line anti-seizure agents for total of six days. Patients who fail to respond to initial blinded treatment (SAGE-547 or placebo) may be eligible to be treated with an open-label, higher dose regimen of SAGE-547	This was an open-label study consisting of a Screening period (1 day), 4-day treatment period (96 hours) followed by a 1-day dose taper period (24 hours), a 2-day acute follow-up period, and a 3-week extended follow-up period
Follow-up	Individual follow-up of 21 days following initiation of study treatment.	Active treatment period for up to 96 hrs, follow-up period 29 days.
Primary outcome/s	Success or failure, with success defined as weaning the subject off all third-line agents before completion of the blinded infusion of SAGE-547 or placebo, and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the blinded infusion of SAGE-547 or placebo, and concurrent signs of physiologic brain	Safety and tolerability of SAGE-547 including, adverse events, physical and neurological examinations as assessed by the National Institutes of Health Stroke Scale (NIH-SS), EEG, vital signs, clinical laboratory measures, ECG, and concomitant medication usage, will be evaluated

	activity as determined by EEG (primary response).	
Secondary outcome/s		Efficacy of SAGE-547 on super-refractory status epilepticus as indicated by the need to re-institute a continuous IV AED (third-line agent), for refractory seizure control as well as the duration of the observed response; Pharmacokinetics (PK) of SAGE-547 exposure, Functional Status: mRS-9Q; Clinical Global Impression of Severity and Improvement; Glasgow Coma Scale; RASS; Survival.
Key results	-Not available; trial ongoing	- Efficacy: Seventeen of the 22 subjects (77%) in the efficacy population were classified as responders in this study. - Safety: A total of 23 subjects (92%) experienced at least 1 TEAE. Six subjects (24%) died in the study related to underlying condition. Sixteen subjects (64%) experienced at least 1 SAE. None of which was determined by the Safety Committee to be related to SAGE-547.
Adverse effects (AEs)	- Not available; trial ongoing	See above
Expected reporting date	Topline results expected in 3 rd quarter, 2017	Primary completion date reported as Jun 2015

ESTIMATED COST and IMPACT

COST

The cost of SAGE-547 is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS and CARERS

- | | |
|--|---|
| <input checked="" type="checkbox"/> Reduced mortality/increased length of survival | <input type="checkbox"/> Reduced symptoms or disability |
| <input type="checkbox"/> Other | <input type="checkbox"/> No impact identified |

IMPACT ON HEALTH and SOCIAL CARE SERVICES

- | | |
|---|---|
| <input type="checkbox"/> Increased use of existing services | <input type="checkbox"/> Decreased use of existing services |
| <input type="checkbox"/> Re-organisation of existing services | <input type="checkbox"/> Need for new services |
| <input type="checkbox"/> Other | <input checked="" type="checkbox"/> None identified |

IMPACT ON COSTS and OTHER RESOURCE USE

- | | |
|--|--|
| <input type="checkbox"/> Increased drug treatment costs | <input type="checkbox"/> Reduced drug treatment costs |
| <input checked="" type="checkbox"/> Other increase in costs: <i>new treatment option for this population</i> | <input checked="" type="checkbox"/> Other reduction in costs |
| <input type="checkbox"/> Other | <input type="checkbox"/> None identified |

OTHER ISSUES

- | | |
|---|---|
| <input type="checkbox"/> Clinical uncertainty or other research question identified | <input checked="" type="checkbox"/> None identified |
|---|---|

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Appendix F: Protocols for treating convulsive status epilepticus in adults and children. Available from: <https://www.nice.org.uk/guidance/cg137/chapter/Appendix-F-Protocols->

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