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

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Primary objective:To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in subjects with SRSE, and for the response to endure at...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON43720

Source
ToetsingOnline

Brief title
STATUS trial

Condition

- Other condition
- Seizures (incl subtypes)

Synonym
epilepsy, seizures

Health condition

Epilepsy

Research involving
Human

Sponsors and support

Primary sponsor: SAGE Therapeutics
Source(s) of monetary or material Support: SAGE Therapeutics

Intervention

Keyword: Double-blind, randomised, SAGE-547, SRSE

Outcome measures

Primary outcome

Success or failure, with success defined as weaning the subject off all third-line agents before completion of the first 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 first infusion of SAGE-547 or placebo, and concurrent signs of physiologic brain activity as determined by EEG (primary response).

Secondary outcome

1. The time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;

2. Secondary response, defined as success of weaning the subject off all third-line agents before the end of the first SAGE-547 or placebo infusion;

3. The time between meeting the secondary response endpoint, defined in (2)

above, and the reinstitution of any third-line agent for seizure or burst

suppression up to Visit 12;

4. The assessment of clinical status as measured by change in the CGI from

Visit 1 (Screening) to Visit 12;

5. The number of days after the end of the first study drug infusion that the

subject does not have status epilepticus, up to Visit 12;

6. The number of days after the end of the first study drug infusion that the

subject does not have seizures (convulsive and non-convulsive) up to Visit 12;

7. The number of separate episodes of status epilepticus occurring up to Visit

12;

8. The proportion of subjects with a new diagnosis of epilepsy after Visit 11.

Study description

Background summary

Epidemiology of SRSE
The incidence of SRSE is very poorly understood, mainly because the diagnostic codes used for SE do not generally differentiate its nature as responding or refractory to treatment. Based on the variable reporting of outcomes data, the incident cases of SRSE could represent between one and two-thirds of the RSE patients (Novy, Logroscino et al. 2010; Ferlisi and Shorvon 2012; Hocker, Britton et al. 2013; Sutter, Marsch et al. 2013). More detailed epidemiology studies are needed to better elucidate the proportion of RSE patients whose condition becomes super-refractory. A recent review of ICU discharge data in the USA suggests an annual incidence of approximately 35,000, based on patients who required at least three days in the ICU for SE [Sage data on file].
Outcomes of SRSE
SE has varying degrees of mortality depending on the underlying etiologies. The mortality rate of SRSE is estimated to be 30% to 50% using current standard of care.
The causes of death from SE (and therefore SRSE) are heterogeneous, resulting from neuronal cell death, complications of underlying medical conditions, or adverse effects of the current standard treatments. Prognosis worsens and

mortality increases with longer duration of SE, i.e. with SE that develops into RSE or SRSE (Neligan and Shorvon 2010), and with longer duration of medically-induced coma (Ferlisi and Shorvon 2012). There is an obvious unmet medical need to improve upon the current standard of care treatment regimens. Morbidity is high and survivors have outcomes ranging from poor function to vegetative state (Shorvon 2011). Approximately one third of patients with RSE and SRSE will recover, but with chronic neurologic or other deficits (Neligan and Shorvon 2010; Hocker, Britton et al. 2013). In all, it is estimated that less than 25-30% of all SRSE patients have a favorable functional outcome.
Unmet Medical Need in Super-refractory Status Epilepticus
Treatment approaches for SRSE consist of diagnosis and treatment of underlying medical conditions, adding and changing anti-seizure drugs, and repeated attempts at weaning from IV anesthetic agents. Treatment of SRSE has three aims:
* to prevent excitotoxicity, which begins within 24 hours of SE onset;
* to prevent cerebral damage by initiating neuroprotective burst suppression;
* to prevent the complications of extended periods of anesthesia or unconsciousness (Shorvon 2011).
Currently, there are no therapies that have been specifically approved for RSE or SRSE. The primary drugs used to induce coma are continuously infused IV anesthetics such as propofol, midazolam, or pentobarbital, known as third-line agents. Use of these drugs to control SRSE has only been studied in small retrospective reviews or small prospective studies without controls (Hocker, Britton et al. 2013) therefore there is no agreement on which drug is optimal nor on an optimal dosing regimen for the treatments that are used.
The most common adverse effect of the third-line agents is hemodynamic instability; in addition, they are not universally effective, with breakthrough seizures and withdrawal seizures requiring dose adjustments and changes in third-line agent(s). The drug thought to be most effective in SRSE, pentobarbital, is also associated with the most toxic adverse effect profile, comprising decreased blood pressure and cardiorespiratory collapse (Claassen, Hirsch et al. 2002). The ability to wean patients successfully off the third-line agents as quickly as possible is therefore paramount, and an adjunct to SRSE treatment that enhances the success of the third-line agents and supports their successful weaning in a short timeframe would be an important addition to the therapeutic armamentarium. Preliminary clinical data show that SAGE-547 has been a successful adjunct to third-line therapy in this regard.
For more information refer to the study protocol paragraph 3 page 27.

Study objective

Primary objective:
To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in subjects with SRSE, and for the response to endure at least 24 hours after the end of the SAGE-547 or placebo infusion (primary response).
Secondary objectives:

1. To compare between SAGE-547 and placebo the time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. To compare between SAGE-547 and placebo secondary response, defined as success of weaning the subject off all third-line agents before the end of the first infusion of SAGE-547 or placebo;
3. To compare between SAGE-547 and placebo the time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. To compare the change in the Clinical Global Impression scale (CGI) between SAGE-547 and placebo up to Visit 12;
5. To determine the number of days after the end of the first infusion of study drug that the subject does not have status epilepticus, up to Visit 12;
6. To determine the number of days after the end of the first infusion of study drug that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. To determine the number of separate episodes of status epilepticus occurring up to Visit 12;
8. To determine the proportion of subjects with a new diagnosis of epilepsy after Visit 11.

Study design

This is a randomized, double-blind, placebo-controlled trial, designed to evaluate the efficacy and safety of SAGE-547 administered as a continuous intravenous infusion to subjects in SRSE.
Patients will follow one of three paths to entry to the study.
1)The first path is for subjects who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst or seizure suppression with a third-line agent.
2)The second path to entry to the study is for subjects who have either been transferred from another hospital or from within the study site institution and who are already on a continuous intravenous infusion of thirdline agent with a burst or seizure suppression pattern on the EEG. These subjects may have had one or more previous unsuccessful weans and may be on more than one third-line agent.
3)The third path to entry to the study is for subjects who have either been transferred from another hospital or from within the study site institution and who arrive at the study site intensive care unit without a burst or seizure suppression pattern on the EEG or not on a continuous infusion of at least one third-line agent. These subjects may have had one or more previous unsuccessful weans.

Once subjects are deemed to be failures of the QW, they must be randomized to SAGE-547 or placebo in a 1:1 ratio and the blinded study drug infusion commenced within eight hours of the investigator*s determination that they

failed the QW.

The randomized portion of the study will be blinded, with the two treatments (SAGE-547 and placebo) being indistinguishable so that subjects, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

For all subjects in the study, attempts will be made to wean the subject off all third-line agents starting at hour (H) 49 of the blinded study treatment infusion, with the aim of completing all weans by hour (H) 120 of the study treatment infusion.

Those subjects who fail the primary endpoint, and require re-institution of a third-line agent regimen before the end of the blinded study drug infusion or within 24 hours of completing the blinded study drug infusion will be eligible to receive an open-label infusion of SAGE-547 at a dose higher than that administered in the blinded part of the study.

Intervention

Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within six hours of the investigator*s determination that they failed the QW.

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo.

For all subjects in the study, attempts will be made to wean the subject off all third-line agents starting at hour (H) 49 of the blinded study treatment infusion, with the aim of completing all weans by hour (H) 120 of the study treatment infusion. Blinded study treatment infusion is a period 6 days (144hrs).

Subjects who fail the primary endpoint, and require re-institution of a third-line agent regimen before the end of the blinded study drug infusion or within 24 hours of completing the blinded study drug infusion will be eligible to receive an open-label infusion of SAGE-547 at a dose higher than that administered in the blinded part of the study.

The same weaning process and study treatment infusion of a period of 6 days (144hrs) will be applied.

Study burden and risks

There may or may not be a direct benefit to the patient from taking part in

this study. The possible benefits of SAGE-547 may include some level of seizure control and the ability to help get the patient off the medications to control their seizures that make him/her unconscious. However, there is no guarantee that the patient will have any benefit. The information gained from the study may benefit medical knowledge and other patients in the future.

Taking part in this study may involve some known risks, discomforts, or inconvenience. There also may be risks that are unknown or unforeseeable. Significant new findings that might affect the decision to continue the participation in the study, will be provided to the subject/LAR.
A small number of healthy human patients have received allopregnanolone, the most common side effects noted in these studies were:
* sleepiness or tiredness
* feelings of intoxication (being drunk)
* flushing (red in the face or neck)
* mild headache

Some of the less common side effects included:
* decreased eye movements
* impaired memory

SAGE-547 has been studied in one study with SRSE patients. Of the 20 patients treated, there were side effects reported in three (3) patients which the study doctor thought might be due to SAGE-547:
* One (1) patient had muscle weakness
* One (1) patient had increased platelets in the blood
* One (1) patient had elevated liver enzymes

There is always a chance that an unexpected or serious side effect may happen. It is also possible to experience a serious allergic reaction which could become life-threatening or fatal.
The standard anti-seizure medications, as well as the study medication will be given intravenously throught a catheter, that may cause pain or discomfort. There is also the risk of infection, bleeding and/or bruising at the insertion site.
Blood Samples as well will be collected using a catheter; the amount collected will be about 81 mL or 150 in case the retreatment is necessary. The patient may have discomfort or pain when blood is collected, and may feel faint or pass out if they are conscious at the time. There is a risk of infection, bleeding, soreness, blood clots, tenderness, or bruising at the puncture site. The patient may develop a small scar at the puncture site where multiple blood samples are taken.
As part of standard of care, a urinary catheter will be placed during the time the patient is unconscious. There is a risk of infection with the placement of a catheter.

Contacts

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Subjects 18 years of age and older.
2. Subjects who have:
* Failed to respond to the administration of at least one first-line agent (e.g., benzodiazepine or other emergent initial AED treatment), according to institution standard of care, and;
* Failed to respond to at least one second-line agent (e.g., phenytoin, fosphenytoin, valproate, phenobarbital, levetiracetam or other urgent control AED), according to institution standard of care, and;
* 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 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.

Exclusion criteria

1. Subjects who are pregnant.
2. Subjects with a known allergy to progesterone or allopregnanolone or any excipients in SAGE-547.
3. Subjects with SRSE due to anoxic/hypoxic encephalopathy with highly malignant/malignant EEG features (Westhall, Rosetti et al. 2016).
4. Subjects who have any of the following: a. a GFR low enough to warrant dialysis but for whatever reason, dialysis that would adequately remove Captisol® is not planned; b. severe cardiogenic or vasodilatory shock requiring two or more pressors that is not related to third-line agent use; c. fulminant hepatic failure; d. no reasonable expectation of recovery (for instance, a likely outcome is persistent vegetative state) or life-expectancy, in the opinion of the investigator, of less than 30 days;
5. Subjects who are being administered more than three third-line agents concomitantly or in whom the qualifying wean cannot be completed within 24 hours, or who are being administered a third-line agent for other indications such as management of raised intra-cranial pressure that would preclude weaning according to this protocol.
6. Subjects with a living will that does not allow heroic measures.
7. Subjects who have been exposed to an investigational medication or device within 30 days; the exception to this is that participation in the Established Status Epilepticus Treatment Trial or ESETT within 30 days of screening for the 547-SSE-301 trial is allowed.
8. Subjects who have been treated or randomized in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not have received study drug/placebo and then re-enroll).

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-08-2016
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	not available yet
Generic name:	not available yet

Ethics review

Approved WMO Date:	06-11-2015
Application type:	First submission
Review commission:	METC Twente (Enschede)
Approved WMO Date:	12-05-2016
Application type:	First submission
Review commission:	METC Twente (Enschede)
Approved WMO Date:	20-05-2016
Application type:	Amendment
Review commission:	METC Twente (Enschede)
Approved WMO Date:	09-06-2016
Application type:	Amendment
Review commission:	METC Twente (Enschede)
Approved WMO Date:	16-08-2016
Application type:	Amendment
Review commission:	METC Twente (Enschede)
Approved WMO	

Date:	24-01-2017
Application type:	Amendment
Review commission:	METC Twente (Enschede)
Approved WMO Date:	03-02-2017
Application type:	Amendment
Review commission:	METC Twente (Enschede)
Approved WMO Date:	04-05-2017
Application type:	Amendment
Review commission:	METC Twente (Enschede)
Approved WMO Date:	10-05-2017
Application type:	Amendment
Review commission:	METC Twente (Enschede)
Approved WMO Date:	02-08-2017
Application type:	Amendment
Review commission:	METC Twente (Enschede)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2015-002142-31-NL
ClinicalTrials.gov	NCT02477618

Register	ID
CCMO	NL54982.044.15

Study results

Date completed: 12-07-2017

Actual enrolment: 0

Summary results

Trial is onging in other countries