Sage Therapeutics, Inc. (SAGE)
Overhyped Lead Drug Headed for Failure

Sage Therapeutics is a pre-commercial pharma firm whose market value stems almost entirely from a single drug – a member of a class of naturally occurring compounds called neurosteroids – in a single indication, a condition called super-refractory status epilepticus (SRSE). SRSE is characterized by repeated or protracted seizures that defy multiple lines of treatment. Thanks to superficially strong results from a small Phase 1/2 trial that lacked a control group, investors have come to view Sage’s drug as “de-risked,” complacently expecting a clear-cut victory when the larger, placebo-controlled Phase 3 trial reads out in the second half of this year.

We disagree. Sage’s drug, a proprietary formulation of the neurosteroid allopregnanolone that the company calls SAGE-547, is little more than a Band-Aid, achieving, at best, a temporary reduction in brain activity – very similar to many other treatments that doctors already use. But SAGE-547 leaves the underlying causes of SRSE untouched. We believe that, in Phase 3, SAGE-547 will fail to outperform placebo to a statistically significant degree, throwing Sage’s future into question. Moreover, a thorough analysis of the scientific literature suggests that Sage’s estimates of the size of the SRSE market are inflated by a factor of 6; thus, even if SAGE-547 does manage to produce passable data, its commercial prospects are far murkier than the market appreciates. As a result, Sage is worth little more than its cash balance, 70% below the current stock price.

While Sage touts SAGE-547 as a novel breakthrough, its high-level mechanism of action – tipping the balance of brain activity from excitation toward inhibition – is exactly the same as that of standard drugs like benzodiazepines, anti-epileptics, and anesthetics that already form the standard of care for status epilepticus. Sage argues that its compound is special because it can affect a specific category of receptors (extrasynaptic GABA₆ receptors) and thereby influence a different form of inhibition (tonic rather than phasic). However, a large body of scientific research clearly shows that many other drugs used in SRSE, including the anesthetics midazolam and propofol, also bind to extrasynaptic GABA₆ receptors. SAGE-547 is not special.

Sage also contends that its Phase 1/2 results were so strong that they could not be “an artifact of serendipity.” Yet our review of the literature shows that the chances that patients recover from even very severe bouts of status epileptics are actually quite good; one large, ongoing study found that 74% of patients recovered. In light of these results, SAGE-547 appears to contribute very little to standard treatments, paving the way for a Phase 3 failure. The firm may be Sage, but its big bet on an unexceptional drug will likely prove unwise.

Disclaimer: As of the publication date of this report, Kerrisdale Advisers, LLC (“Kerrisdale”), other research contributors, and others with whom we have shared our research (the “Authors”) have short positions in the stock of Sage Therapeutics, Inc. (the “Company”), and stand to realize gains in the event that the price of the stock decreases. Following publication, the Authors may transact in the securities of the Company. The Authors have obtained all information herein from sources they believe to be accurate and reliable. However, such information is presented “as is,” without warranty of any kind – whether express or implied – and without any representation as to the results obtained from its use. All expressions of opinion are subject to change without notice, and the Authors do not undertake to update this report or any information contained herein. Please read our full legal disclaimer at the end of this report.
# Table of Contents

I. INVESTMENT HIGHLIGHTS .................................................................................................................................................. 3

II. COMPANY OVERVIEW .................................................................................................................................................. 5

III. SAGE-547 IS A BAND-AID .......................................................................................................................................... 6

IV. SAGE-547 IS MORE OF THE SAME ............................................................................................................................ 8

V. SAGE-547’S CLINICAL RESULTS ARE LESS THAN MEETS THE EYE ........................................................................ 11
   - Recovery from SRSE Is Common ................................................................................................................................. 12
   - SAGE-547’s Results Are Overstated .............................................................................................................................. 15

VI. SAGE-547’S ADDRESSABLE MARKET MAY BE DRAMATICALLY SMALLER THAN THE MARKET REALIZES .................. 17
   - Status Epilepticus Is Less Common Than Sage Claims ................................................................................................ 18
   - Status-Epilepticus Treatments Are More Effective Than Sage Claims ........................................................................ 19

VII. CONCLUSION ......................................................................................................................................................... 23

VIII. REFERENCES ......................................................................................................................................................... 24

FULL LEGAL DISCLAIMER .................................................................................................................................................. 27
I. Investment Highlights

**SAGE-547 is more of the same.** While Sage management naturally touts its lead drug as a great advance, the truth is far more prosaic. As one group of researchers put it, “Many of the behavioural and physiological effects of allopregnanolone [*the active ingredient in SAGE-547*] are similar to those of benzodiazepines and other positive modulators of the GABA-A receptor, such as barbiturates and ethanol” (1). All of these drugs act to strengthen the brain’s existing inhibitory mechanisms in similar ways, and patients with super-refractory status epilepticus (SRSE) have, by definition, received many of them already. Indeed, as we discuss below, some of Sage’s own data demonstrate that SAGE-547 tends to have little physiological impact in such patients: soon after receiving the drug, many patients experienced no change or even an adverse change in their suppression ratios (an electrographic measure of inhibition), and even the positive responses were modest in size.

Sage’s story is that its drug is unique because it binds to GABA\(_A\) receptors not just at synapses but beyond them, in the so-called extrasynaptic region of the neuronal membrane, where such receptors can generate a steady (“tonic”) form of inhibition that differs from the better-known spikes of “phasic” inhibition. But, while it’s true that most benzodiazepines, which constitute the first line of treatment in SRSE, don’t bind to most extrasynaptic GABA\(_A\) receptors, many other standard drugs for treating SRSE do, especially general anesthetics. In Sage’s Phase 1/2 trial, the most common anesthetics used were midazolam, propofol, pentobarbital, and ketamine; every one of these drugs has been shown to bind to extrasynaptic GABA\(_A\) receptors and strengthen tonic inhibition,\(^1\) just like SAGE-547 aims to do. It’s just not that special.

**SAGE-547 is, at best, a Band-Aid.** By the time patients with status epilepticus are classified as super-refractory, their doctors have already tried and failed to suppress their abnormal brain activity in many different ways, and when they turn to general anesthetics they typically succeed, putting the patients into comas and ending their overt seizures. But this is just a temporary fix, buying time in the hope that the underlying disturbance in the network – the cause of which could range from a traumatic injury to a tumor to an autoimmune attack – resolves itself. No one believes that general anesthesia is itself a cure.

SAGE-547 is no different – another way to temporarily suppress brain activity and give patients a chance to heal. It can’t rewire axons. But why would a new, slightly different Band-Aid help patients who already had access to many others – and why would it fetch a high price, as Sage bulls expect?

\(^1\) Illustrative citations:
- “[A]naesthetic agents, for example, *propofol*, have also been demonstrated to act at extrasynaptic receptors and enhance tonic inhibition” (14)
- “Like other GABA\(_A\) receptors, δ-containing receptors [*the main class of extrasynaptic receptors*] are also allosterically potentiated by barbiturates such as pentobarbital” (13)
- “The tonic conductance in cultured hippocampal neurons is enhanced by the benzodiazepine *midazolam*” (15)
- “The NMDA antagonist *ketamine* has recently been demonstrated to be a weak potentiator of GABA\(_A\) receptors with some selectivity for the α6β2/3δ [*extrasynaptic*] receptor subtype. In addition, at concentrations above 100 μM, ketamine could directly activate these receptors” (13)
**SAGE-547’s clinical results are less than meets the eye.** All of SAGE-547’s clinical efficacy data come from studies with no placebo groups; indeed, we suspect that Sage management tried and failed to convince the FDA to allow its ongoing pivotal Phase 3 trial to similarly eschew appropriate controls. Nonetheless, Sage argues that the 77% response rate that its drug achieved in a 25-patient Phase 1/2 trial is too good to attribute to chance. However, that 77% figure reflects the company’s own definition of “evaluable” patients, which excludes “[p]atients…[whose] treatment was disrupted or if no weaning attempts from general anesthesia were made.” A patient who received a partial infusion of SAGE-547 yet remained too fragile to risk taking off of anesthesia thus wouldn’t count against Sage’s skewed measure of success, obviously biasing it toward optimism. On a gold-standard “intent to treat” basis, SAGE-547’s response rate was only 68%. And even that overstates the apparent long-term success rate: 24% of “responders” went on to experience additional bouts of status epilepticus in the following four weeks; meanwhile, 40% of “non-responders” were ultimately weaned off of general anesthesia, apparently no thanks to SAGE-547, which disappears from a patient’s body within a few hours. Overall, four weeks after the treatment period, only 52% of the intent-to-treat population had *and sustained* positive “responses.”

Are these figures impressive? A large 2012 meta-analysis showed that, for patients with refractory status epilepticus – most of whom appear to have progressed to the super-refractory stage – ~65% recovered (2). An ongoing prospective study for which preliminary results were published just last summer – the Global Audit of Treatment of Refractory Status Epilepticus – reported a 74% recovery rate (3).

Against this backdrop, SAGE-547’s results look downright ordinary, especially in light of the great discretion doctors have when deciding when and how to try to wean patients off of anesthesia. After all, for heavily sedated patients coming off of such powerful drugs, unusual brain activity is common, and there is no clear definition of a “seizure” or widely accepted guideline for when to give up and restore the anesthesia. Taking a more aggressive approach to weaning – curtailing anesthesia and then holding off on putting patients back on it even if there are some signs of trouble – can inflate short-term “success” measures without truly affecting long-term outcomes. Viewed in this light, SAGE-547’s early-stage data line up with its “me too” mechanism of action, showing, at best, modest incremental benefits that will likely prove too small to reach statistical significance in Phase 3.

**SAGE-547’s addressable market may be dramatically smaller than the market realizes.** Sage management contends that there are 25,000 annual cases of SRSE in the US, and the sell side has dutifully accepted this claim at face value. When we attempted to reconcile this figure with the scientific literature, however, we came up with a much lower estimate – just 4,000 cases. Sage’s lofty estimate draws primarily on a single epidemiological study of a single small city from 1996 – a study clearly regarded as an unrepresentative outlier by other researchers in the field. Thus, even if SAGE-547 does manage to outperform placebo in Phase 3, its commercial prospects look dim. Making matters worse, Marinus Pharmaceuticals – a sort of sister company for Sage, whose scientific founder has been heavily involved in Sage’s research and whose main drug is a synthetic version of Sage’s – plans to enter the status-epilepticus market with its own extremely similar treatment.

**Sage’s pipeline has little value.** For Sage, SRSE and SAGE-547 are the main event; the company’s other drugs and targeted indications are all very early-stage. Past research has highlighted the risks posed by the development of tolerance to allopregnanolone (SAGE-547’s active ingredient) after chronic use, including *increased* susceptibility to seizures (1; 4). In fact,
highly similar neurosteroids like pregnanolone and minaxolone, intended to serve as anesthetics, have failed to win clinical adoption in part because of convulsive and other excitatory side effects (5; 6; 7). Moreover, because neurosteroids’ mechanism of action closely resembles that of existing drugs like benzodiazepines, it won’t be enough to outperform placebo; Sage will have to outperform its cheap, reliable, well-understood cousins as well. Thus we believe that, outside of SRSE, SAGE-547 and any “next-generation” versions thereof offer high risk and low reward, leaving little value for Sage’s shares.

II. Company Overview

<table>
<thead>
<tr>
<th>Sage Therapeutics: Capitalization and Financial Results</th>
<th>Financial Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>($ in mm except share price)</td>
<td>2015</td>
</tr>
<tr>
<td>Capitalization</td>
<td></td>
</tr>
<tr>
<td>Share price</td>
<td>$ 33.40</td>
</tr>
<tr>
<td>Diluted shares*</td>
<td>32.7</td>
</tr>
<tr>
<td>Market cap</td>
<td>$ 1,091</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Financial Results</td>
<td></td>
</tr>
<tr>
<td>Cash*</td>
<td>$ 327</td>
</tr>
<tr>
<td>Net income</td>
<td>$ (95)</td>
</tr>
<tr>
<td>Free cash flow</td>
<td>(71)</td>
</tr>
</tbody>
</table>

*Pro forma for January 2016 equity raise. Assumes greenshoe wasn’t exercised. †Consensus estimates via Capital IQ.

Sage was founded in 2010 with the mission of treating brain disorders using allosteric receptor modulators – drugs that, rather than directly activate or block receptors, instead alter the strength of their effects. The plan didn't progress quickly; in fact, Sage’s current CEO initially turned down the job because, in the words of one press report, it “didn’t sound like [Sage] had yet identified promising molecules as potential drugs.” In late 2013, however, Sage licensed data and materials pertaining to the compound allopregnanolone from the University of California and entered into an agreement with Ligand Pharmaceuticals to use its Captisol product to make allopregnanolone more water-soluble. Allopregnanolone formulated in Captisol for intravenous use is what Sage now calls SAGE-547, the company’s main drug.

Allopregnanolone is a naturally occurring compound synthesized from the sex hormone progesterone. It belongs to a class of substances called neurosteroids – steroids that affect brain function through their influence on neurotransmitter receptors, including the inhibitory GABA_A receptor. The idea of harnessing such substances for medical purposes is by no means new. To the contrary, 19 years ago, one researcher traced the history of "water-soluble steroid hypnotic[s]" back to 1927 but lamented that such drugs never proved worthwhile, especially in light of the alternatives:

[W]e are therefore left to wonder whether it is likely that any steroid anaesthetic agent will have a pharmacological profile superior to other i.v. [intravenous] induction agents presently available. (emphasis added) (6)
Allopregnanolone was not exempt from this skepticism. Fifteen years ago, a group of researchers, noting that neurosteroids “are currently considered as having a future role in the management of epilepsy, anxiety, insomnia, migraine and drug dependence,” found that repeated administration of allopregnanolone in mice led to tolerance, ultimately making it ineffective against seizures. The researchers concluded:

Collectively, the results of this study, along with recently published data...indicate similar pharmacological and side-effects profiles of benzodiazepines and neurosteroids. Moreover, a similar efficacy of allopregnanolone and midazolam [a benzodiazepine] has been found. These findings, together with the conversion of neurosteroids in the brain to other steroid hormones (testosterone, estradiol, and aldosterone), add to the accumulating evidence suggesting a less favorable pharmacological profile for this class of drugs than was previously thought. (emphasis added) (8)

By the late 1990s, a biotech firm called CoCensys, which had been working on a synthetic form of allopregnanolone called ganaxolone for use as an anticonvulsant therapy, suspended development, and its equity lost almost all of its value before being sold to Purdue Pharma for ~$7.5 million. In 2004, Marinus Pharmaceuticals purchased the rights to ganaxolone (9), but the company has struggled to produce convincing clinical results. Today, despite its strong similarities and direct links to Sage, Marinus trades for just one-tenth of Sage’s market cap and has seen its stock price fall 50% in the past twelve months.

Notwithstanding the checkered history of neurosteroids in medicine, Sage began in 2012 to test allopregnanolone on patients with super-refractory status epilepticus, relying on special “emergency use” rules; it then commenced a formal (albeit small, single-arm, and open-label) Phase 1/2 clinical trial in January 2014. In spring 2015, Sage completed its IPO and announced the results of the trial, touting them as “unprecedented.” A few months later, it began its 140-patient, placebo-controlled Phase 3 trial, which it expects to yield top-line data by the second half of this year.

III. SAGE-547 Is a Band-Aid

The condition that SAGE-547 is supposed to treat is really a symptom, not a disease. While having a seizure at some point in one’s life is relatively common, typical seizures don’t last long; in patients with status epilepticus (SE), on the other hand, seizures are either protracted (five minutes is a common benchmark) or recurrent. The causes of SE vary widely, from stroke to cerebral tumor to meningitis to something unknown (so-called cryptogenic SE). The mortality rate appears to vary widely as well: one study found that anoxic SE, in which the brain loses access to oxygen as a result of e.g. cardiac arrest, has the highest mortality rate (51%), while

---

2 For example, one of Marinus’s scientific founders, Michael Rogawski, was an early Sage advisor and created some of the allopregnanolone-related intellectual property later licensed by Sage.
withdrawal from antiepileptic drugs in patients with epilepsy has the lowest mortality rate (10%) (3).

The standard first line of treatment for status epilepticus consists of benzodiazepines like lorazepam and diazepam – drugs that, just like SAGE-547, enhance the effects of the inhibitory GABA\textsubscript{A} receptor and thereby reduce brain activity. While benzodiazepines and neurosteroids like SAGE-547 bind to different allosteric sites on the receptor and favor different forms of the receptor (GABA\textsubscript{A} receptors are each composed of five different sub-units selected from a menu of 19, creating many possible “isoforms”), the underlying mechanisms are extremely similar.

In many patients, benzodiazepines quickly terminate status epilepticus. But some patients progress to what is sometimes called established status epilepticus and receive second-line treatment in the form of anti-epileptic drugs like phenytoin or valproate. If that doesn’t work, patients are classified as “refractory” and proceed to the third line of treatment: general anesthesia, most often in the form of propofol, midazolam, or pentobarbital. After 24 hours, doctors usually attempt to wean refractory patients off of anesthesia, and many emerge seizure-free, albeit often in poor neurological condition. But if the seizures come back, the patients, now classified as super-refractory, go back on general anesthesia, often in five-to-seven-day cycles punctuated by additional weaning attempts, which often succeed.

What this treatment paradigm shows is that, by the time patients have reached super-refractory status, temporarily “pausing” their brains doesn’t address the underlying network disturbance. Benzodiazepines, anti-epileptics, and anesthetics have all done their part to shift the balance from excitation toward inhibition, yet once the drugs are tapered off, the seizures return; some entrenched anomaly – for instance, an injury that healed incorrectly, wreaking havoc on the brain’s delicate wiring – is still there. Strengthening the inhibitory GABA system – as benzodiazepines, anesthetics, and SAGE-547 all do in slightly different ways – can make individual cells quiet down, but it does nothing to address the higher-level problem.

This perspective is shared by the many doctors and researchers intimately familiar with SRSE with whom we have spoken. In the words of one of them, “If a person is coming in because they have antibodies attacking NMDA receptors, or intracranial hemorrhage, or traumatic brain injury, the allopregnanolone is not going to have any impact on the cause.” Another put it succinctly: “So much of long-term survival and outcomes depends on what the underlying etiology of the disease is.” In other words, both allopregnanolone (SAGE-547) and existing treatments can only hope to buy time and give patients a chance to recover on their own; for instance, an autoimmune attack causing repeated seizures might spontaneously end. But the treatments themselves have no enduring benefits. This is especially true for allopregnanolone, which has a brief half-life of about an hour,\(^3\) implying that, within four to five hours of administration, it effectively vanishes. It can only enhance inhibition while it’s actually binding to a GABA\textsubscript{A} receptor. When it’s gone, the normal (lower) level of inhibition resumes, and, if the underlying

\(^3\) See e.g. Sage’s 2014 10-K, p. 11: “The pharmacological properties of SAGE-547, including a short half-life of one hour, allows for continuous IV administration” (emphasis added).
problem generating the seizures still exists, that level of inhibition may not be enough to keep the seizures in check.

In short, giving SAGE-547 (or anesthetics) credit for SRSE patients’ recoveries is like giving a Band-Aid credit for the healing of a wound. The Band-Aid just kept the problem from getting worse; the wounded person’s own endogenous mechanisms were what actually fixed it. Band-Aids are useful, of course, but they’re already cheap and widely available; a slightly different type of Band-Aid is not going to garner much interest, let alone earn a massive price premium. SAGE-547’s very premise is thus inherently flawed.

IV. SAGE-547 Is More of the Same

To counter the natural conclusion that, relative to existing treatments for SRSE, SAGE-547 has little to offer, Sage tells a reassuring story suggesting that SAGE-547 is special after all. As Sage’s CEO recently put it:

SAGE-547 modulates GABA\(_A\). It’s called a positive allosteric modulator of GABA\(_A\), and it basically serves to calm the brain down. It does so through a unique mechanism. So most of us are familiar probably either professionally or personally with benzodiazepines; they help you sleep, and they are allosteric modulators of GABA\(_A\). They however work at one part of the brain called the synaptic receptor. That receptor has a characteristic which is not helpful for chronic therapy or in the setting of severe disease, and that is the synaptic GABA\(_A\) receptor basically leaves the membrane surface in the setting of protracted seizures or even in the setting of long-term treatment.

So, if you remember, benzodiazepines – after a time they wear off, and people have to dose-escalate. In the patients that we treat – I mentioned this earlier – all of them are by definition benzodiazepine failures, and they fail, primarily, we believe, because the GABA\(_A\) synaptic receptor goes away. SAGE-547 is distinct in that it works at the extrasynaptic receptor. That receptor remains on the surface even in the setting of long-term seizure. And so if you want to increase inhibitory tone through a GABA\(_A\) mechanism, you need to do it through extrasynaptic modulation, which is what SAGE-547 does.\(^4\)

While this story has elements of truth, it conveniently glosses over several problems. First, while the loss of synaptic GABA\(_A\) receptors may contribute to benzodiazepine resistance in SRSE, it’s far from settled science that it actually does. In fact, researchers at Tufts University – whom

Sage’s CEO has cited approvingly in a different context\(^5\) – have argued that benzodiazepine resistance actually stems from dysfunctions in chloride homeostasis and can be reversed in animal models using drugs that target chloride transport \((10; 11)\). If the underlying problem is just a loss of synaptic receptors, as Sage sweepingly pronounces, then why would an approach that doesn’t bring those receptors back have any effect? Moreover, if the loss of synaptic receptors makes benzodiazepines useless, how is it that the most commonly used anesthetic in Sage’s own Phase 1/2 trial, the benzodiazepine midazolam, succeeded in keeping patients in medically induced comas?

Not only does Sage exaggerate the strength of the hypothesis that extrasynaptic receptors are crucial in treating SRSE; it also fails to mention that many drugs besides SAGE-547 also bind to extrasynaptic receptors. In the words of one review:

> During the past decade, the emergence of tonic inhibitory conductance in extrasynaptic GABA\(_A\)Rs has coincided with evidence showing that these receptors are highly sensitive to the sedatives and hypnotics used in anesthesia. \((12)\)

While it’s true that benzodiazepines don’t bind to the most widely discussed type of extrasynaptic receptor – the \(\delta\) subunit–containing receptor, a key target for neurosteroids like SAGE-547 – there are other types of extrasynaptic receptors that they can bind to, like \(\alpha_5\beta_2\) receptors \((13)\). Meanwhile, many general anesthetics also work primarily by affecting GABA\(_A\) receptors, including extrasynaptic ones. All of the anesthetics commonly used in treating SRSE, including propofol, barbiturates, midazolam, ketamine, and etomidate, have been shown to bind to extrasynaptic receptors and enhance the tonic form of GABA-mediated inhibition \((13; 14; 15; 16)\). In addition, experimental drugs like ganaxolone, gaboxadol (THIP), magnolol, honokiol, and certain benzamide compounds also have the same effect: binding to extrasynaptic receptors and enhancing tonic inhibition \((17; 18; 19)\).

In light of all this evidence, it’s clear that, far from having a “unique mechanism,” SAGE-547 and its active ingredient, allopregnanolone, are more of the same. In fact, the anesthetic midazolam even appears to increase the synthesis of endogenous allopregnanolone, making the subsequent introduction of foreign allopregnanolone even less likely to matter \((20; 21)\).\(^6\) By definition, patients with super-refractory status epilepticus have already received general anesthetics. As a result, their extrasynaptic GABA\(_A\) receptors have already been modulated. If strengthening the effects of these receptors were enough to fix their seizures, they would already be fixed. The notion that SAGE-547 is so novel that it can do significantly more than ordinary anesthetics makes no sense.

\(^5\) Bloomberg transcript of Sage presentation at the Piper Jaffray Healthcare Conference, December 2, 2015 (“there were animal data that show – [a] woman [named] Jamie Maguire [at] Tufts has done nice knockout work, showing that you can make a silent knockout of extrasynaptic modulation in rats…”).

\(^6\) While recent work has suggested that midazolam’s impact on allopregnanolone synthesis does not contribute to its antiseizure activity \((48)\), this finding should not comfort Sage. After all, if increased allopregnanolone production confers no measurable benefits, why should adding yet more allopregnanolone do anything either?
Since SAGE-547 is more of the same, giving it to patients who are already on general anesthetics and anti-epileptics shouldn’t have a large physiological effect. Indeed, that’s what Sage’s own EEG data show, though Sage has dutifully argued the opposite. Below is a graph that Sage presented at the annual meeting of the American Epilepsy Society in December. The x-axis shows different concentrations of SAGE-547 (measured in nanomoles per liter) in patients’ plasma at different points in time shortly after they received the drug. The y-axis shows the percentage change in the “suppression ratio,” defined as “the instantaneous probability of the total power dropping below 3 μV [microvolts]” as measured by the EEG. The suppression ratio is supposed to serve as a biomarker for patients’ ability to resist any flare-up in brain activity. An increase in the suppression ratio relative to its baseline level might imply that a drug like SAGE-547 is working (although it’s unclear whether a 10% move in the suppression ratio from, say, 50% to 55% is truly clinically meaningful).

While Sage attempts to depict these data as demonstrating a tight dose/response relationship – higher plasma concentrations of SAGE-547 giving rise to larger increases in the suppression ratio – the correlation is visibly weak. Without the three points in the upper right, showing patients with measured SAGE-547 plasma concentrations in the 400-450 nanomolar range, there would be no apparent correlation at all. But these concentrations are far higher than the steady-state levels that Sage actually targets; in the Phase 1/2 trial, the “standard dose” was 200 nM and the “higher dose” was 300 nM. The relevance of the >400nM data points is thus unclear.

In addition, Sage starts the y-axis below zero, making it somewhat difficult to notice just how many instances there are of negative changes in the suppression ratio, implying that many patients experienced more high-power EEG readings after receiving SAGE-547 – the opposite of the goal. In the revised version of the graph below, we block out the >400nM data points and restore the y=0 line:

---

7 The “higher dose” group actually performed worse than the “standard dose” group (67% response rate vs. 81%), a troubling data point in its own right.
Within and below the range of concentrations that Sage aims for, there is no clear
dose/response relationship at all, and there are about as many observed values below zero as
above. When the likelihood of even short-term EEG improvement is little better than a coin toss,
and low doses work as well as high doses, it’s difficult to believe that SAGE-547 is adding much
value. Nor, in view of the drug’s more-of-the-same mechanism of action, should anyone expect it to.

V. SAGE-547’s Clinical Results Are Less than Meets the Eye

If SAGE-547 is so similar to existing SRSE therapies, why do investors have high expectations
for it? The main answer is that the drug’s Phase 1/2 results look good: 17 out of 22 “evaluable”
patients “were successfully weaned off of all third-line agents during the SAGE-547
maintenance period,” and the same number “were successfully weaned off both the third-line
agents [anesthetics] and SAGE-547 without recurrence of SE in the 24-hour period following
treatment.”8 Sage presents this as a 77% response rate.

---

8 Kanes et al., “Results of Phase 1/2 Trial of SAGE-547 for Super-Refractory Status Epilepticus (547-
SSE-201): Response and Relationship to Underlying Patient Characteristics,” presented at the 69th
Annual Meeting of the American Epilepsy Society, December 4-8, 2015. We do not believe these two
groups of 17 patients were identical given e.g. the following comment from Sage’s prospectus from July
2014 (p. 2-3), prior to the completion of the trial: “Three of these patients [each of whom was ‘successfully
weaned off his or her anesthetic agent while SAGE-547 was being administered’] were subsequently
weaned off SAGE-547 without reinstating general anesthesia, while one patient experienced
recurrence of SE upon withdrawal of SAGE-547 requiring reinstitution of general anesthesia”
(emphasis added). This fourth patient would qualify as a “responder” by the first criterion but not by the
second.
Of course, the trial didn’t have a placebo group, so whether 77% is actually impressive (especially given the very small sample size) depends on what the appropriate benchmark is. Sage management has argued that 77% is so much better than what could reasonably be expected that its drug must deserve the credit:

So here you have patients with documented treatment failures, who had failed multiple attempts at weaning, so it would be pretty unusual to have – you may get lucky, lucky once or twice, but you get lucky 22 \textit{[sic]} times in a row, I’ll be heading off to Vegas at this point. And so it doesn’t make sense statistically to be a – an artifact of serendipity. So we have these data and we know from the clinical – from the clinical published literature that about the best available therapy suggest 35% response rate in the setting of really good medical therapy. That’s the actual response rate.\textsuperscript{10}

However, we disagree with this characterization of “the clinical published literature” and its implications for Sage. First, relevant benchmarks in the literature suggest that the probability of spontaneous recovery in SRSE is actually fairly high. Second, we believe that Sage’s purported Phase 1/2 response rate of 77% is inflated, consistent with its similarly optimistic and arguably misleading presentation of its earlier emergency-use data.

\textit{Recovery from SRSE Is Common}

Sell-side analysts, apparently taking their cues from Sage management, often claim that patients with SRSE have only a 30-40% probability of emerging from the condition. Often it appears that they’re imposing a strict definition of recovery that requires patients not just to survive seizure-free but to escape any severe disabilities. Given the severity of the underlying etiologies for many with SRSE, as well as the duration of their seizures, many survivors do develop a range of neurological and other maladies. But Sage’s definition of “response rate” makes no reference to disabilities; all it requires is weaning from anesthetics or the cessation of seizures for a brief specified period.

In fact, it’s clear from Sage’s disclosures that many patients who received SAGE-547 and \textit{were counted as successes} nonetheless remained in poor health. For example, Patient #2 from SAGE-547’s emergency-use data set was “a previously healthy 11 year old female”; after discontinuation of SAGE-547, she had “reduced” seizure activity and, one week later, “was awake and following commands” – hardly a complete recovery. Patient #4 was weaned off midazolam within 24 hours of receiving SAGE-547 but “was found to have significant brain atrophy.” Patient #6, also counted as a success, emerged from SRSE but was still in the early stages of recovery: “Her EEG is normalizing and she is beginning to respond to simple commands.” Meanwhile, in the Phase 1/2 trial, Patients #1 and #3 also fell short of total

\textsuperscript{9} At best, Sage “got lucky” 17 times; getting lucky 22 times would imply a 100% response rate.

\textsuperscript{10} Bloomberg transcript of Sage presentation at the Goldman Sachs US Emerging & Smid-Cap Growth Conference, November 19, 2015.
recovery despite meeting the “key efficacy endpoint”: the former was “discharged to a rehabilitation facility to continue recovery,” while the latter “remained hospitalized to continue to be treated for severe ongoing medical conditions.”

In short, since Sage’s own definition of a “response” to its drug doesn’t require the responder to survive unscathed, the appropriate benchmark to use when evaluating SAGE-547 is not how many patients with SRSE end up completely healthy; it’s how many patients survive and stop having long or recurrent seizures.

One of the best sources of information on this question is a 2012 meta-analysis by Monica Ferlisi and Simon Shorvon, researchers at University College London’s Institute of Neurology, entitled “The outcome of therapies in refractory and super-refractory convulsive status epilepticus and recommendations for therapy” (2). The authors compile data from more than a thousand patients drawn from more than 100 published studies and conclude:

We found control of refractory and super-refractory status epilepticus in 74% (678/920) of the reported cases.

The table below indicates seizure control rates of 64% for the barbiturate anesthetics thiopental and pentobarbital, 78% for midazolam, and 68% for propofol:

![Ferlisi & Shorvon 2012: “Overall Outcome of Anaesthetic Therapy”](source.png)

While it’s true that this review includes refractory and not just super-refractory patients, we can infer from the reported median durations of therapy that the average patients on thiopental or pentobarbital and propofol actually were super-refractory; otherwise, the period of anesthesia would have been shorter. For thiopental/pentobarbital and propofol, the median durations of therapy were 53 and 32 hours, respectively, while, for midazolam, it was only 16 hours.\(^\text{11}\) Even if we therefore discard midazolam’s 78% control rate as potentially unrepresentative of super-refractory (as opposed to merely refractory) SE, the base rate still appears to be 64-68%.

\(^{11}\) Assuming a Poisson distribution for duration of therapy, we estimate that >90%+ of the patients in each of those two groups are super-refractory.
The meta-analysis also includes information on longer-term outcomes in refractory SE, showing that 65% of patients survive, and more than half of the survivors recover to their previous neurological baseline:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>207(35%)</td>
</tr>
<tr>
<td>Severe neurological deficit</td>
<td>79 (13%)</td>
</tr>
<tr>
<td>Mild neurological deficit</td>
<td>80 (13%)</td>
</tr>
<tr>
<td>Undefined neurological deficit</td>
<td>22 (4%)</td>
</tr>
<tr>
<td>Recovery to baseline</td>
<td>208 (35%)</td>
</tr>
</tbody>
</table>

In the reports of 596 cases (51% of the total of 1168), the long-term outcome was recorded. In the other 575 cases, no long-term outcome data were provided.

Source: Ferlisi & Shorvon 2012 (2)

Similarly, a large, ongoing, prospective study of refractory status epilepticus, led in part by the same researchers responsible for the meta-analysis, reported the following preliminary results (3):

We were able to classify 413 patients into these three categories, while for 75 patients, the final outcome of the status epilepticus was considered missing because of the lack of sufficient data: **304 patients recovered from status epilepticus (74%),** 93 patients died (22%), and 16 patients had the therapy actively withdrawn (4%).

While these data again combine refractory and super-refractory patients, the available information on the duration of patients’ stays in intensive-care units (ICUs) suggests that most cases were severe, with 69% of stays exceeding 7 days:

<table>
<thead>
<tr>
<th>Total ICU stay</th>
<th>N</th>
<th>% out of 353</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;7 days</td>
<td>108</td>
<td>31</td>
</tr>
<tr>
<td>7–14 days</td>
<td>99</td>
<td>28</td>
</tr>
<tr>
<td>15–29 days</td>
<td>79</td>
<td>22</td>
</tr>
<tr>
<td>30–59 days</td>
<td>51</td>
<td>14</td>
</tr>
<tr>
<td>60–210 days</td>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>353</td>
<td>100</td>
</tr>
</tbody>
</table>

Source: Ferlisi et al. 2015 (3)
Overall, the perception created by Sage that only a third of SRSE patients ever recover is badly exaggerated; the true number is likely double that. In a population of only 22 “evaluable” patients, the difference between 77% and 65% amounts to just three patients – a number that, contrary to Sage’s protests, is easy to attribute to “serendipity.”

**SAGE-547’s Results Are Overstated**

Not only are the chances of recovery from SRSE on standard therapies better than Sage bulls would like to believe; the results from Sage’s key Phase 1/2 trial are also worse. While Sage trumpets its 77% “response rate,” that figure uses as its denominator a sub-group of 22 “evaluable” patients, not the 25 patients actually enrolled in the trial.

The intuitive interpretation of the term “evaluable” is that a patient is non-evaluable if, for some reason, doctors cannot evaluate his or her condition. In reality, however, Sage’s definition of “evaluable” excludes “[p]atients…[whose] treatment was disrupted or if no weaning attempts from general anesthesia were made.” Thus patients who received the drug but clearly failed to improve (or even deteriorated), making their doctors unwilling to roll the dice by weaning them off anesthesia, would not be deemed “evaluable” and would not count against Sage’s “response rate.” Common sense, of course, would dictate that, if one gives a patient a drug in the hopes of ending anesthesia, only to find that doing so still seems so risky it’s not worth trying, that should count as evidence that the drug is ineffective. In Sage’s rose-tinted world, however, such data points are swept under the “non-evaluable” rug.

Fiddling with denominators to inflate reported success rates is a trick that biotech investors are all too familiar with; that’s why clean “intent to treat” statistics, which factor in enrolled patients irrespective of convenient excuses about why their weak results shouldn’t count, are strongly preferred. On an intent-to-treat basis, SAGE-547’s response is not 77% (17/22) but 68% (17/25).

In addition, 24% of the “responders” (4 out of 17) experienced “recurrence of status epilepticus” in the four weeks after the treatment period; in those cases (at a minimum), SAGE-547 clearly did not have a long-lasting effect. Furthermore, 40% of the “non-responders” (2 out of 5) actually did recover enough to go off of anesthesia\(^\text{12}\) – not because of any benefit from SAGE-547 (which, because of its short half-life, was long gone from their bodies) but for the same reasons that many such patients spontaneously recover. Counting only the 13 “responders” with no SE recurrences during the follow-up period, SAGE-547’s **sustained** response rate was only 52% (13/25).

Sage indulged in similar “grade inflation” when presenting the results of its emergency-use experience (not a formal clinical trial but a small group of patients treated with SAGE-547 after

\(^{12}\) See Sage’s presentation at Antiepileptic Drug and Device Trials XIII, May 2015: “2 non-responder group ultimately were weaned off GA” (slide 7).
exhausting their other options). Sage sought to take credit for patients whose status epilepticus resolved as long as three days after they stopped receiving SAGE-547. Given the drug’s one-hour half-life, it’s impossible that it had anything to do with such patients’ recoveries; when we asked one doctor about it, he replied, “The pharmacology really doesn’t make sense for that to do it, no.”

SAGE-547’s results are even less impressive in light of the great discretion doctors have in determining how to attempt to wean patients off of anesthetics and what to do when early signs of trouble appear. What counts as a seizure isn’t as clear-cut as it may seem; after coming off of anesthesia, many patients have abnormal EEG activity but no overt physical convulsions. In such situations, whether to reinstitute anesthetics is a judgment call. A very cautious doctor might reinstitute anesthetics quickly, even knowing that many patients in the same condition manage to recover; a more aggressive doctor might hold off, take a calculated risk, and give the patient a chance to stabilize. Aggressive weaning can therefore create the appearance of better results without actually changing long-term outcomes.

Such considerations matter when interpreting a single-arm, open-label trial. In a randomized, placebo-controlled, double-blind trial like SAGE-547’s ongoing Phase 3, however, there is far less scope for generating superficially good yet spurious results. Interestingly, based on sell-side reports, it appears that Sage tried and failed to convince the FDA to commit to approve SAGE-547 on the basis of a comparison to “historical data” rather than a true control group. It’s tempting to conclude that the company was wary of pitting its drug head-to-head against the standard of care – a very reasonable fear, given SAGE-547’s undistinguished mechanism of action and the high underlying rate of spontaneous recovery in SRSE.

In sum, we believe that SAGE-547’s physiological effects, though real, are temporary and add little to no value to existing treatments for SRSE. Since the Phase 3 trial will explicitly compare the two, we expect that SAGE-547 will fail to produce statistically and clinically significant results, and the drug will be regarded as a dead end, just like similar neurosteroids after many years of research.

13 See e.g. its July 2014 prospectus, p. 88-90.
14 Animal models also confirm that the antiseizure activity of allopregnanolone, the active ingredient in SAGE-547, is short-lived; see e.g. Rogawski et al. 2013 (49).
15 See e.g. the Leerink note dated 12/8/14 (“The company is unsure whether or not the agency [the FDA] will require a placebo in Phase III or if it will allow SAGE to perform an open-label trial and compare ‘547’s efficacy to natural history”) and the SunTrust Robinson Humphrey note dated 1/26/15 ( “This valuation scenario would entail a 70% probability of success for SAGE-547 in SRSE in the U.S. based on promising results to date, and the FDA agreeing on the use of historical data as comparator for a pivotal trial”).
VI.  SAGE-547’s Addressable Market May Be Dramatically Smaller than the Market Realizes

While we believe that SAGE-547 will fail to significantly outperform placebo in the Phase 3 SRSE trial, statistical flukes are always possible. If we assume that the drug somehow does come to market, how big is the commercial opportunity?

Sage management asserts that about 25,000 patients per year in the US develop SRSE. Our analysis of the scientific literature, however, points to a far lower number – just 4,000. It is thus quite possible that, even if SAGE-547 wins approval, its sales will disappoint investors on a massive scale.

The chart below compares Sage’s view of the market opportunity to ours. In the text that follows, we detail our underlying sources and assumptions. While no one has an unimpeachable estimate of the frequency of SRSE – including Sage – the market’s heretofore complacent attitude on this issue means that the risks are clearly to the downside.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Sage</th>
<th>Kerrisdale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Status epilepticus (SE)</td>
<td>150,000</td>
<td>46,000</td>
</tr>
<tr>
<td>Established SE</td>
<td>50,000</td>
<td>16,000</td>
</tr>
<tr>
<td>Refractory SE</td>
<td>35,000</td>
<td>8,000</td>
</tr>
<tr>
<td>Super-refractory SE</td>
<td>25,000</td>
<td>4,000</td>
</tr>
</tbody>
</table>

Source: Kerrisdale analysis
**Status Epilepticus Is Less Common Than Sage Claims**

The structure of Sage’s estimation process is reasonable: first, the company estimates the incidence of status epilepticus overall; then, it estimates the incidence of established SE as a subset of SE; then, it estimates the incidence of refractory SE as a subset of established SE; and, finally, it estimates the incidence of super-refractory SE as a subset of refractory SE. The problem is that Sage’s assumed parameter values often differ substantially from the best available published evidence.

For instance, Sage’s primary source for the claim that there are ~150,000 cases of status epilepticus per year in the US is a 20-year-old journal article by DeLorenzo et al. (22). The authors conducted a prospective study of SE cases in the city of Richmond, Virginia, from 1989 to 1991 and identified 41 patients per 100,000 individuals per year.

This estimate, however, is a huge outlier, as the table below demonstrates:

<table>
<thead>
<tr>
<th>Lead author</th>
<th>Pub. Date</th>
<th>Period covered</th>
<th>Geography</th>
<th>Total cases</th>
<th>Freq. per 100k</th>
<th>Standardized or crude?</th>
<th>Mortality rate</th>
<th>Extrapolated US cases</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>DeLorenzo</td>
<td>1996</td>
<td>1989-1991</td>
<td>Richmond, VA</td>
<td>166</td>
<td>41.0</td>
<td>crude</td>
<td>22.0%</td>
<td>161,550</td>
<td>(22)</td>
</tr>
<tr>
<td>Hesdorffer</td>
<td>1998</td>
<td>1965-1984</td>
<td>Rochester, MN</td>
<td>199</td>
<td>18.3</td>
<td>standardized</td>
<td>n/a</td>
<td>59,127</td>
<td>(23)</td>
</tr>
<tr>
<td>Jallon</td>
<td>1999</td>
<td>1997-1998</td>
<td>Geneva</td>
<td>61</td>
<td>15.5</td>
<td>crude</td>
<td>6.6%</td>
<td>50,081</td>
<td>(24)</td>
</tr>
<tr>
<td>Coeytaux</td>
<td>2000</td>
<td>1997-1998</td>
<td>French Switzerland</td>
<td>172</td>
<td>10.3</td>
<td>standardized</td>
<td>7.6%</td>
<td>33,279</td>
<td>(25)</td>
</tr>
<tr>
<td>Knake</td>
<td>2001</td>
<td>1997-1999</td>
<td>Germany</td>
<td>150</td>
<td>17.1</td>
<td>standardized</td>
<td>9.3%</td>
<td>51,050</td>
<td>(26)</td>
</tr>
<tr>
<td>Vignatelli</td>
<td>2003</td>
<td>1999-2000</td>
<td>Bologna</td>
<td>44</td>
<td>10.7</td>
<td>standardized</td>
<td>39.0%</td>
<td>34,572</td>
<td>(28)</td>
</tr>
<tr>
<td>Vignatelli</td>
<td>2005</td>
<td>1999-2001</td>
<td>Northern Italy</td>
<td>27</td>
<td>11.6</td>
<td>standardized</td>
<td>7.4%</td>
<td>37,480</td>
<td>(29)</td>
</tr>
<tr>
<td>Chin</td>
<td>2006</td>
<td>2002-2004</td>
<td>London</td>
<td>226</td>
<td>14.5</td>
<td>crude</td>
<td>3.0%</td>
<td>46,850</td>
<td>(30)</td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>14.5</td>
<td>crude</td>
<td>8.5%</td>
<td>46,850</td>
<td></td>
</tr>
<tr>
<td>Average ex. DeLorenzo &amp; Wu (equal-weighted)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>14.0</td>
<td>12.4%</td>
<td>45,234</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average ex. DeLorenzo &amp; Wu (case-weighted)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>14.8</td>
<td>10.6%</td>
<td>47,729</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Source:** Kerrisdale analysis  
**Note:** assumes US population of 323.1 million.
While DeLorenzo et al. find a status-epilepticus frequency of 41 per 100,000, eight other studies, covering a range of populations and periods, put the number at 6 to 18, with a central tendency of ~14.5 – dramatically lower and consistent with a few tens of thousands of cases per year in the US, not hundreds of thousands.

While the reasons for this discrepancy are not clear, one likely factor is race. The population of Richmond, Virginia, studied by DeLorenzo et al. was 43% white and 57% “nonwhite,” primarily black; the frequency of SE was 2.9x higher for nonwhites than whites, an imbalance also observed in other studies (27; 30). Yet DeLorenzo et al. did not attempt to adjust their estimated frequency to correspond to the overall racial makeup of the US, which today is only 28% nonwhite (13% black). More speculatively, Richmond’s statistics may have been skewed upward by the crack-cocaine epidemic, which hit the city hard during the period when DeLorenzo et al. were gathering their data; one local news story in 2012 referred to this era as “the bad old days, when 11 homicides a month were typical and the annual body count was always in the 100s, when crack-cocaine-induced drug wars ripped this city apart.” While straightforward drug overdoses and head trauma are not major direct causes of status epilepticus as reported by DeLorenzo et al., crack may have had indirect effects; for example, cocaine is known to increase the risk of stroke (31), which in turn increases the risk of SE.

Whatever the explanation, it’s clear that the study most frequently cited by Sage is not representative of the totality of the available literature and forms a very weak foundation for additional extrapolation. Indeed, relative to our disagreement regarding the overall frequency of status epilepticus, our other disagreements with Sage over its estimation assumptions (detailed below) are minor.

Furthermore, while we treat older and newer studies as equivalent, some researchers have raised the possibility that the frequency of status epilepticus has declined over time. Wu et al., whose study of California is summarized in the table above but flagged as potentially unrepresentative because it focused on a single sub-type of SE (generalized convulsive SE or GCSE), found that the rate of GCSE fell 42% between 1991 and 1998 (27):

Our finding that the incidence of GCSE has steadily decreased over the last decade supports the notion that GCSE may be less common now than in the past.

If this trend has continued to the present day, then Sage’s estimated SRSE market size may be even more inflated than it seems.

**Status-Epilepticus Treatments Are More Effective Than Sage Claims**

Of the ~30-60,000 patients per year treated for status epilepticus, how many fail to respond to first-, second, and third-line treatments, thus marking them as super-refractory and potentially eligible for SAGE-547? We compiled evidence from a host of academic publications, summarized in the table below.
### Success Rates for Status-Epilepticus Treatments

<table>
<thead>
<tr>
<th>Lead author</th>
<th>Pub. date</th>
<th>Period covered</th>
<th>Total case</th>
<th>Patients</th>
<th>Avg. age</th>
<th>Epil. history</th>
<th>1st line/ treatment</th>
<th>2nd line/ treatment</th>
<th>3rd line/ treatment</th>
<th>Coma induction</th>
<th>RSE freq.</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novy(^{10})</td>
<td>2010</td>
<td>2006-2008</td>
<td>128</td>
<td>118</td>
<td>59</td>
<td>58%</td>
<td>Clonazepam(^2)</td>
<td>Phenytoin/valproate(^2)</td>
<td>Various(^4)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Mayer(^{8,8})</td>
<td>2002</td>
<td>1994-1998</td>
<td>83</td>
<td>74</td>
<td>63</td>
<td>38%</td>
<td>Benzos</td>
<td>Phenytoin(^2)</td>
<td>Phenobarbital</td>
<td>31%</td>
<td>54%</td>
<td>58%</td>
</tr>
<tr>
<td>Holtkamp(^{11})</td>
<td>2005</td>
<td>1993-2002</td>
<td>83</td>
<td>79</td>
<td>53</td>
<td>40%</td>
<td>Benzos</td>
<td>Phenytoin/fosphen.</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Rossetti</td>
<td>2005</td>
<td>1997-2004</td>
<td>127</td>
<td>107</td>
<td>NA</td>
<td>90%</td>
<td>Benzos</td>
<td>Phenytoin(^2)</td>
<td>Various(^7)</td>
<td>NA</td>
<td>NA</td>
<td>74%</td>
</tr>
<tr>
<td>Sage(^{16})</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Benzos</td>
<td>AEDs</td>
<td>Anesthetics</td>
<td>65%</td>
<td>30%</td>
<td>29%</td>
<td>23%</td>
</tr>
<tr>
<td>Treiman</td>
<td>1998</td>
<td>1990-1995</td>
<td>384</td>
<td>384</td>
<td>NA</td>
<td>42%</td>
<td>Lorazepam</td>
<td>Phenobarbital</td>
<td>Diazepam &amp; Phenytoin</td>
<td>65%</td>
<td>58%</td>
<td>56%</td>
</tr>
<tr>
<td>Appletan(^{12})</td>
<td>1995</td>
<td>1992</td>
<td>61</td>
<td>61</td>
<td>&lt;6</td>
<td>63%</td>
<td>Lorazepam</td>
<td>Diazepam</td>
<td>NA</td>
<td>96%</td>
<td>85%</td>
<td>NA</td>
</tr>
<tr>
<td>Leppik</td>
<td>1983</td>
<td>NA</td>
<td>70</td>
<td>70</td>
<td>53</td>
<td>70%</td>
<td>Lorazepam</td>
<td>Diazepam</td>
<td>NA</td>
<td>89%</td>
<td>76%</td>
<td>NA</td>
</tr>
<tr>
<td>Cock</td>
<td>2002</td>
<td>1995-1998</td>
<td>72</td>
<td>72</td>
<td>51</td>
<td>79%</td>
<td>Lorazepam</td>
<td>Diazepam</td>
<td>LZP &amp; DZP</td>
<td>65%</td>
<td>61%</td>
<td>67%</td>
</tr>
<tr>
<td>Misra</td>
<td>2006</td>
<td>NA</td>
<td>68</td>
<td>68</td>
<td>NA</td>
<td>NA</td>
<td>Valproate</td>
<td>Phenytoin</td>
<td>Valproate &amp; Phenytoin(^{14})</td>
<td>66%</td>
<td>42%</td>
<td>58%</td>
</tr>
<tr>
<td>Gilad</td>
<td>2008</td>
<td>NA</td>
<td>74</td>
<td>74</td>
<td>53</td>
<td>NA</td>
<td>Valproate</td>
<td>Phenytoin</td>
<td>NA</td>
<td>88%</td>
<td>88%</td>
<td>NA</td>
</tr>
<tr>
<td>Alvarez</td>
<td>2011</td>
<td>2006-2010</td>
<td>187</td>
<td>187</td>
<td>62</td>
<td>55%</td>
<td>Valproate</td>
<td>Phenytoin</td>
<td>Levetiracetam</td>
<td>75%</td>
<td>59%</td>
<td>52%</td>
</tr>
<tr>
<td>Agarwal</td>
<td>2007</td>
<td>2004-2006</td>
<td>100</td>
<td>100</td>
<td>27</td>
<td>NA</td>
<td>Valproate</td>
<td>Phenytoin</td>
<td>NA</td>
<td>88%</td>
<td>84%</td>
<td>NA</td>
</tr>
<tr>
<td>Uberall</td>
<td>2000</td>
<td>NA</td>
<td>41</td>
<td>41</td>
<td>&lt;18</td>
<td>NA</td>
<td>Valproate</td>
<td>NA</td>
<td>NA</td>
<td>78%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Claassen(^{9})</td>
<td>2001</td>
<td>1970-2001</td>
<td>193</td>
<td>193</td>
<td>48</td>
<td>34%</td>
<td>Midazolam</td>
<td>Propofol</td>
<td>Pentobarbital</td>
<td>37%</td>
<td>54%</td>
<td>57%</td>
</tr>
<tr>
<td>Hayashi</td>
<td>2007</td>
<td>1991-2002</td>
<td>358</td>
<td>358</td>
<td>49</td>
<td>54%</td>
<td>Midazolam</td>
<td>NA</td>
<td>NA</td>
<td>65%</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

**Source:** Kerrisdale analysis
Notes:

1. Age has been directly correlated to mortality rates in SE cases. Results may be skewed towards failure in studies with high average ages.
2. Primary but not exclusive treatments.
3. Mayer study showed selection bias: patients were pre-screened for being in ICU to begin with. This likely had an adverse effect on reported efficacy of first-line treatment.
4. Third-line treatment varied by patient and included thiopental, propofol, midazolam, and ketamine.
5. According to Novy et al. (32), a history of epilepsy is associated with a lower risk of reaching refractory status epilepticus. Only 12 patients required coma induction.
6. Mayer, Holtkamp, and Rossetti are all retrospective studies using patients at ICUs, who typically have worse prognoses than ordinary patients (including anoxic patients).
7. Many patients were given more than one third-line treatment.
8. In the Mayer study, the mean seizure time prior to emergency-department admission was 1.3 hours, which may have skewed the data adversely.
9. This was a retrospective study that included the results from 28 other studies, most of which had <10 patients. The % of patients with history of epilepsy was unusually low, artificially increasing the effective morbidity rates.
10. In the Novy study, RSE was defined as SE continuing after administration of a second-line SE treatment (typically either phenytoin or valproate). However, rather than inducing a coma for patients who failed second-line treatment, many patients were instead given another anti-epileptic drug instead.
11. The Holtkamp study results are skewed due to exclusively looking at NICU patient records; patients not refractory to early treatments would not be transferred to NICU.
12. The Appletan study was exclusive to children. Average age was <6 years old. Using IV results, excluding rectal administration. The study also appears to have included regular seizures, which would tend to inflate the success rates.
13. Success rate for the Claassen study is defined as no withdrawal seizures.
14. This patient group refers to the patients who were refractory to either valproate or phenytoin and subsequently received the other drug during this trial.
15. No patients died within 24 hours, but patients died while in the hospital: 11 patients died within the first week, 6 in the second week, and 2 in the third week.
16. See e.g. Sage's July 2014 prospectus, p. 86. The implied first-line-treatment success probability is (150k-50k)/150k = 67% (but verbally approximated as 65%). The implied second-line-treatment success probability is (50k-35k)/50k = 30%. The implied third-line-treatment success probability is (35k-25k)/35k = 29%. The implied rates of RSE and coma induction as a fraction of SE are both 35k/150k = 23%.
At 65%, Sage’s estimated first-line (benzodiazepine) response rate (shown in the “Sage” row of the table above) does look roughly consistent with the literature. For second-line therapy, however, its assumption appears far too pessimistic. Sage claims that second-line (anti-epileptic) therapy is effective at controlling status epilepticus in only 30% of patients. Yet in our review of the literature, focusing on studies published in the past 30 years and involving more than 10 patients, we couldn’t find a single study with an efficacy rate that low. To the contrary, studies consistently pointed to efficacy rates higher than 50% for patients refractory to first-line treatment (33; 42; 43; 44).

In addition, one study furnished evidence of even greater efficacy from *multiple* second-line drugs administered concurrently: even when the first second-line drug failed, the probability that a second such drug succeeded was 58% (40). In another study, of 30 patients classified as “refractory,” only 40% actually required coma induction, implying that the other 60% ultimately responded to additional rounds of first- or second-line treatments (32). Overall, we conclude that second-line treatment succeeds in at least 50% of cases. The better early-stage treatment works, the fewer patients will progress to super-refractory status, shrinking the market for SAGE-547.

Similarly, Sage appears to have underestimated how many refractory patients respond to their first round of general anesthesia. In the aggregate, the large studies we located reported a success rate of 298 out of 490 patients, or 61%,16 more than double Sage’s tacit assumption of 29%.17 While there are many small studies involving only a handful of patients, thus creating opportunities for cherry-picking, we believe 50% is a conservative assumption. Again, the better that patients respond to conventional treatment, the smaller the opportunity for Sage.

In sum, we estimate the frequency of SRSE in the US as follows:

- ~46,000 cases of status epilepticus, of which...
- 65% respond to first-line (benzodiazepine) treatment, leaving...
- ~16,000 cases of established status epilepticus, of which...
- 50% respond to second-line (anti-epileptic) treatment, leaving...
- ~8,000 cases of refractory status epilepticus, of which...
- 50% respond to the first round of general anesthesia, leaving...
- ~4,000 cases of super-refractory status epilepticus, a factor of 6 lower than what Sage assumes.

To be sure, many of the available studies of advanced status epilepticus are small and flawed, making any estimate imprecise, but this stems in part from the underlying rarity of the condition. While Sage has recently suggested that a bespoke, unpublished analysis of insurance-claims

---

16 Derived from Classen et al. (45) (67 successes out of 132 patients assessed) and Hayashi et al. (46) (231 successes out of 358 patients assessed).

17 Sage assumes 35,000 refractory SE patients, of whom 25,000 progress to super-refractory SE, implying that 10,000 recover after a single round of general anesthesia and hence do not progress. 10,000 / 35,000 ≈ 29%.
data lines up with its 25,000-per-year SRSE estimate,\textsuperscript{18} the fact is that there is no explicit insurance code for SRSE, making any such analysis inherently error-prone and subject to bias. It behooves investors to reconcile Sage’s claims to the scientific literature themselves rather than rely on a self-interested management team for guidance. Whatever the true frequency of SRSE is, we believe it’s substantially smaller than Sage would like the market to think, setting the stage for significant disappointment – unless, of course, SAGE-547 never makes it that far in the first place, which we believe is the likeliest outcome.

Muddying the waters even further is Marinus Pharmaceuticals. Marinus’s lead drug, ganaxolone, is a synthetic version of allopregnanolone, the active ingredient in SAGE-547. Marinus is now developing an intravenous form of ganaxolone to treat status epilepticus – putting it in direct competition with SAGE-547. Since the drugs are virtually identical, it’s likely that, if SAGE-547 manages to succeed, so too will ganaxolone, further circumscribing SAGE-547’s commercial opportunity. At the moment, the market gives Marinus little credit for this possibility, ascribing its equity only $93 million of value, less than one-tenth of Sage’s market cap. This large gap in implied optimism is one measure of the market’s faith that SAGE-547 is somehow special and can defy the odds – a faith that our analysis shows is profoundly misplaced.

\textbf{VII. Conclusion}

Using neurosteroids to treat disorders of the central nervous system is not a new idea. The problem is that neurosteroids are so similar to other widely used GABAergic agents that there’s little reason to believe they’ll add any value to existing treatments. By harping on the results of a single small, open-label, uncontrolled clinical trial and creating a specious narrative about how its drug is unique, Sage has played a weak hand very well, raising expectations ahead of its Phase 3 results. But given SAGE-547’s “more of the same” mechanism of action and the high rate of recovery achieved by standard treatments, we expect the drug to fail. Even if it succeeds, the SRSE market is no great prize and will likely prove to be far smaller than the market believes. With the company’s current valuation built entirely on hope, the downside is enormous.

\textsuperscript{18}See e.g. Sage’s February 2016 investor presentation (no long available online), slide 12.
VIII. References


18. The natural products magnolol and honokiol are positive allosteric modulators of both synaptic and extra-synaptic GABA<sub>A</sub> receptors. Alexeev, Mikhail, et al. 8, June 2012, Neuropharmacology, Vol. 62, pp. 2507-2514.


Full Legal Disclaimer

As of the publication date of this report, Kerrisdale Advisers, LLC and its affiliates (collectively "Kerrisdale"), others that contributed research to this report and others that we have shared our research with (collectively, the “Authors”) have short positions in the stock of Sage Therapeutics, Inc. (“SAGE”), and stand to realize gains in the event that the price of the stock decreases. Following publication of the report, the Authors may transact in the securities of the company covered herein. All content in this report represent the opinions of Kerrisdale. The Authors have obtained all information herein from sources they believe to be accurate and reliable. However, such information is presented “as is,” without warranty of any kind – whether express or implied. The Authors make no representation, express or implied, as to the accuracy, timeliness, or completeness of any such information or with regard to the results obtained from its use. All expressions of opinion are subject to change without notice, and the Authors do not undertake to update or supplement this report or any information contained herein.

This document is for informational purposes only and it is not intended as an official confirmation of any transaction. All market prices, data and other information are not warranted as to completeness or accuracy and are subject to change without notice. The information included in this document is based upon selected public market data and reflects prevailing conditions and the Authors’ views as of this date, all of which are accordingly subject to change. The Authors’ opinions and estimates constitute a best efforts judgment and should be regarded as indicative, preliminary and for illustrative purposes only.

Any investment involves substantial risks, including, but not limited to, pricing volatility, inadequate liquidity, and the potential complete loss of principal. This report’s estimated fundamental value only represents a best efforts estimate of the potential fundamental valuation of a specific security, and is not expressed as, or implied as, assessments of the quality of a security, a summary of past performance, or an actionable investment strategy for an investor.

This document does not in any way constitute an offer or solicitation of an offer to buy or sell any investment, security, or commodity discussed herein or of any of the affiliates of the Authors. Also, this document does not in any way constitute an offer or solicitation of an offer to buy or sell any security in any jurisdiction in which such an offer would be unlawful under the securities laws of such jurisdiction. To the best of the Authors’ abilities and beliefs, all information contained herein is accurate and reliable. The Authors reserve the rights for their affiliates, officers, and employees to hold cash or derivative positions in any company discussed in this document at any time. As of the original publication date of this document, investors should assume that the Authors are short shares of SAGE and stand to potentially realize gains in the event that the market valuation of the company’s common equity is lower than prior to the original publication date. These affiliates, officers, and individuals shall have no obligation to inform any investor or viewer of this report about their historical, current, and future trading activities. In addition, the Authors may benefit from any change in the valuation of any other companies, securities, or commodities discussed in this document. Analysts who prepared this report are compensated based upon (among other factors) the overall profitability of the
Authors’ operations and their affiliates. The compensation structure for the Authors’ analysts is generally a derivative of their effectiveness in generating and communicating new investment ideas and the performance of recommended strategies for the Authors. This could represent a potential conflict of interest in the statements and opinions in the Authors’ documents.

The information contained in this document may include, or incorporate by reference, forward-looking statements, which would include any statements that are not statements of historical fact. Any or all of the Authors’ forward-looking assumptions, expectations, projections, intentions or beliefs about future events may turn out to be wrong. These forward-looking statements can be affected by inaccurate assumptions or by known or unknown risks, uncertainties and other factors, most of which are beyond the Authors’ control. Investors should conduct independent due diligence, with assistance from professional financial, legal and tax experts, on all securities, companies, and commodities discussed in this document and develop a stand-alone judgment of the relevant markets prior to making any investment decision.