William Blair

March 20, 2015
Basic Report (15-031)

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Sage Therapeutics, Inc.

A Weaning Therapy in Super Refractory Status Epilepticus; Initiating Coverage With an Outperform Rating and $75 Price Target

Sage Therapeutics is a development-stage biopharmaceutical company focused on therapies for rare central nervous system (CNS) disorders. The company's lead program, SAGE-547, is being developed for the treatment of super-refractory status epilepticus (SRSE), a rare life-threatening condition in which the patient is in a state of persistent seizure, is unresponsive to currently available therapies, and must be placed in a medically induced coma.

Super-refractory status epilepticus affects about 25,000 individuals who have progressed to this state after being unresponsive to treatment with first-line benzodiazepine therapy and second-line antiepileptic drug (AED) therapy. SRSE has a 30% to 50% rate of mortality and morbidity, and SAGE-547 has received emergency-use investigational new drug (IND) status for 10 patient cases to date. Efficacy and safety data for SAGE-547 have been impressive thus far. The company has an ongoing Phase I/II trial in which the primary endpoint of safety and tolerability was achieved in all patients. Of the 17 evaluable patients for efficacy, 71% of patients (12 of 17) achieved the efficacy endpoint of weaning off general anesthetic, while SAGE-547 was being administered and being weaned off SAGE-547 without recurrence of SRSE. Of the nine evaluable emergency-use cases, 78% (7 of 9) of the patients were able to wean off general anesthetic and SAGE-547 with no SRSE and duration of effect grea51.56ter than, or equal to, 24 hours, which is the potential Phase III endpoint.

In addition to emergency-use IND status, the company has received fast-track status, orphan drug designation, and a protocol amendment to their Phase I/II trial to include treatment of pediatric patients as young as two years old and increased dosing of SRSE. Further upside to development timelines may also come from SAGE-547 meeting the FDA's criteria for breakthrough status. We currently project a 2017 approval for SAGE-547 however this timing will be influenced by the company's recent end of Phase II meeting with the FDA. We are initiating coverage of Sage Therapeutics with an Outperform rating and Aggressive Growth profile. Our price target of $75 is based on an NPV analysis of SAGE-547, risk-adjusted 80% for clinical probability of success. We estimate peak sales of SAGE-547 of $1.5 billion by penetrating 65% of the population with SRSE in the United States and 40% of the population in Europe. We do not assign any NPV for the company's pipeline compounds, SAGE-217 and SAGE-689, which would provide upside to our valuation.

Risks involved include regulatory risks surrounding the FDA's guidance on the pivotal study for SAGE-547 as well as competitive risks to the company's pipeline products with several compounds in development for orphan epilepsies.

Sage Therapeutics, based in Cambridge, Massachusetts, is a development-stage biotechnology company focused on therapies for rare central nervous system disorders.

Stock Rating:	**Outperform**
Company Profile:	**Aggressive Growth**
Price Target:	$75
Symbol:	SAGE (NASDAQ)
Price:	$51.56 (52-Wk.: $24–$52)
Market Value (mil.):	$1,331
Fiscal Year End:	December
Long-Term EPS Growth Rate:	NA
Dividend/Yield:	None

Estimates	**2014A**	**2015E**	**2016E**
EPS FY	($1.67)	($3.09)	($2.95)
EBITDA (mil.)	($34)	($64)	($62)

Valuation			
P/E	NA	NA	NA

Trading Data	
Shares Outstanding (mil.)	25.81
Float (mil)	11.63
Average Daily Volume	179,227

Financial Data	
Long-Term Debt/Total Capital	NM
Book Value Per Share	NM
Enterprise Value (mil.)	$1,203

Contents

Company Overview

Sage Therapeutics is a development-stage biopharmaceutical company focused on novel medicines to treat rare CNS disorders. The company's lead product, SAGE-547, is used for the indication of SRSE, a severe disease that affects about 25,000 patients per year and has a 50% mortality rate. Early efficacy signals are strong in this severe patient population and could warrant an accelerated approval and/or FDA breakthrough status for SAGE-547. The company is continuing to enroll a Phase I/II trial for SRSE in an expansion cohort under a protocol amendment that allows pediatric patients as young as two years old and enables increased dosing of SAGE-547. Of the 17 evaluable patients for efficacy from the company's latest data readout, 12 (or 71%) of 17 patients were successfully weaned from their medically induced comas, and all 20 patients enrolled to date have not experienced any drug-related serious adverse events. The company has received emergency-use IND (EIND) status to treat nine additional patients, seven of whom (or 78%) had responded, outside the Phase I/II study.

The company is looking to develop SAGE-547 for additional indications, such as essential tremor, and is also developing two pipeline follow-on candidates, SAGE-689 and SAGE-217. Exhibit 1 shows the company's development pipeline to date.

Exhibit 1
Sage Therapeutics, Inc.
Product Pipeline

Product	Preclinical Development	Phase I	Phase II	Phase III/ Pivotal	Comments/Timing
SAGE-547 (Super-Refractory Status Epilepticus)					End–of–Phase II meeting with the FDA in early 2015 with initiation of pivotal Phase III in mid-2015 for super-refractory status epilepticus
SAGE-547 (Essential Tremor)					Exploratory
SAGE-547 (Severe Postpartum Depression)					Exploratory
SAGE-217					Phase I trial in late 2015, orphan genetic epilepsies (oral)
SAGE-689					Phase I trial in late 2015, adjunctive status epilepticus (IV)
New Chemical Entities					Other CNS disorders – GABA/NMDA

Sources: Company reports and William Blair & Company, L.L.C.

Management has likely met with the FDA for their end–of–Phase II meeting to review the results of its Phase I/II study and emergency-use cases. At this meeting, the company expected to receive guidance for a pivotal Phase III program for SAGE-547 for SRSE. At present, there are no therapies to treat SRSE, and the current standard of care involves placing patients in a medically induced coma and slowly weaning them off, with the hope that the reduced brain activity will lead to a reduction in the seizures that define the disease. The company has already received fast-track status and an orphan indication for SAGE-547, and in exhibit 2 we show the rough timeline of events in 2015 for the company.

Exhibit 2
Sage Therapeutics, Inc.
Timeline and Events

Date	Product	Event	Description/Comments
Near Term	SAGE-547	Regulatory	End–of–Phase II meeting with the FDA and update on pivotal program
Mid-2015	SAGE-547	Clinical	Final data from Phase I/II open-label trial
Mid-2015	SAGE-547	Clinical	Initiate registration trial for SRSE
Mid-2015	SAGE-547	Clinical	Data readout from exploratory Phase IIa essential tremor trial
Mid-2015	SAGE-547	Clinical	Data readout from exploratory Phase IIa severe postpartum depression trial
Late 2015	SAGE-689	Clinical	Initiate Phase I trial
Late 2015	SAGE-217	Clinical	Initiate Phase I trial

Sources: Company reports and William Blair & Company, L.L.C. estimates

We believe that SAGE-547 has shown impressive efficacy to date in patients with a serious unmet medical need for which there are no currently approved therapies. Furthermore, the Phase I/II protocol amendment to treat pediatric patients as young as two years old and EIND patient enrollment leads us to believe that the FDA sees the unmet need and efficacy of SAGE-547 and may grant breakthrough therapy status, which could further accelerate the approval of SAGE-547.

Key Risks

An investment in shares of Sage Therapeutics involves clinical, regulatory, competition, and financial risks that are typical for developmental-stage biopharmaceutical companies. Although we believe that Sage Therapeutics is addressing a significant unmet medical need in SRSE, the company relies heavily on the success of SAGE-547.

Clinical Risk
SAGE-547 has completed a small Phase I/II trial in 12 patients to date, while additional patients are being treated under emergency-use IND filings. While initial response rates in super-refractory patients have been impressive (about 70%), these results will likely need to be replicated in larger patient numbers for SAGE-547 to gain significant traction among neurologists. SRSE is a heterogeneous population with polypharmacy often used in late lines of therapy, so the response rate for SAGE-547 may weaken as the therapy is used in broader patient populations. While our physician discussions suggest that a 50% response rate in truly refractory patients would continue to be impressive, we believe investor enthusiasm for shares may wane if response rates weaken.

Orphan Exclusivity Is Key Protection With Patents Pending
SAGE-547 is a proprietary formulation of allopregnanolone, which is a known metabolite of progesterone, and is not covered under typical composition-of-matter patents associated with new molecular entities. The company has several patent families filed, but these filings likely will take some time to issue, if issued at all. In our valuation for SAGE-547, we assume a sole lifespan of orphan exclusivity of seven years in the United States and 10 years in the European Union for the product. If filed patents are issued and listed in the Orange Book they could provide coverage through 2033.

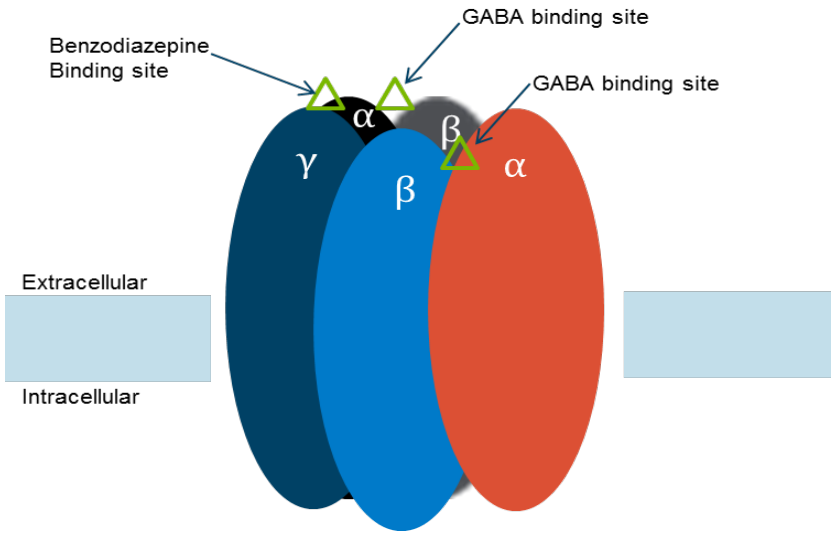
Competitive Risk Potentially Exists for Pipeline Drugs to Treat Orphan Epilepsies
Although we are unaware of any competitive drugs to SAGE-547 for the indication of SRSE, the company expects to launch their clinical programs for their pipeline candidates, SAGE-217 and SAGE-689 by year end in orphan epilepsies. We do believe that these products will be examining disorders for which there are competitive programs; therefore, competitive risk will exist in the development of these compounds.

$GABA_A$ Receptor Overview and Role in Neurological Disease

Before we expand on the role of $GABA_A$ (γ-Aminobutyric acid type A) receptors and the mechanism of action for SAGE-547, we should briefly review nerve-cell signaling. Nerve cells connect with one another at synapses, where release of neurotransmitters and reuptake by target neurons facilitate signaling between the nerve cells. Disruption of the release and/or uptake of these neurotransmitters can meaningfully change many normal processes essential for a healthy life. While small molecules, peptides, and even gases such as nitric oxide can act as neurotransmitters, some common examples include serotonin, which is associated with mood/depression, and epinephrine (adrenaline), which is associated with the fight-or-flight response.

$GABA_A$ receptors are the major inhibitory transmitters in the brain and mediate fast synaptic inhibition (Richter et al, *Nat Chem Biol* 2012). Deficits in these receptors have been shown to be associated with epilepsy, anxiety disorders, cognitive defects, schizophrenia, depression, and substance abuse (Jacob TC et al, *Nat Rev Neurosci* 2008). $GABA_A$ receptor subunits are divided into seven classes (α, β, γ, δ, ε, θ, π), each with several subtypes. A $GABA_A$ receptor in most cases comprises a combination of 2α, 2β, and 1γ or 1δ subunits, and several combinations of these subunits comprise a heterogeneous population of $GABA_A$ receptors, which are potential therapeutic targets (Rudolph U et al, *Annu Rev Pharmacol Toxicol* 2004). A total of 19 $GABA_A$ receptor subunits have been identified in the mammalian brain (Richter et al, *Nat Chem Biol* 2012). Exhibit 3 shows an example of a typical $GABA_A$ receptor that can be found in the brain.

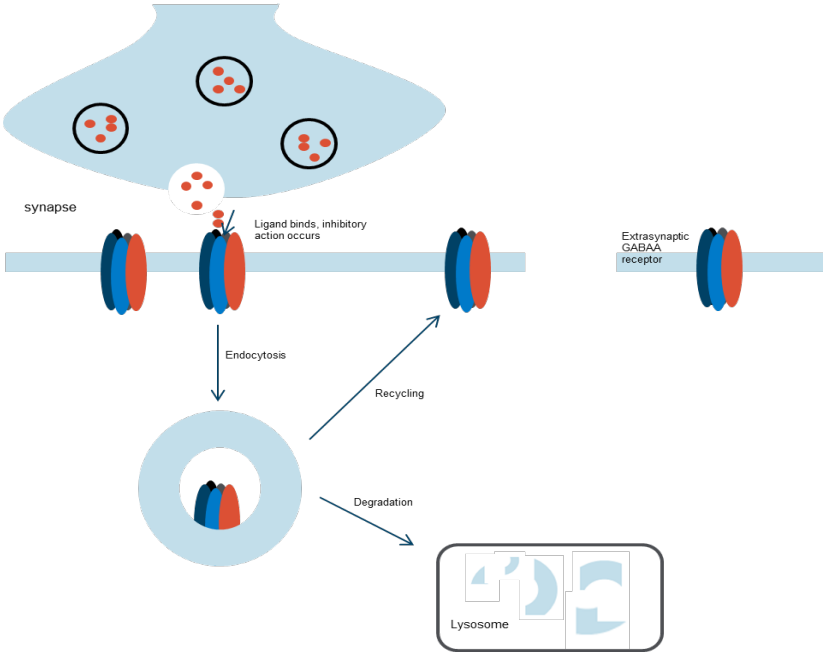
Exhibit 3
Example of $GABA_A$ receptor



Source: Dawson et al. *CNS Spectr.* 2005

Depending on the makeup of the $GABA_A$ receptor, the receptors can be inserted in the cell membrane at the synapse of a neuron (also known as intrasynaptic receptors), where they can have inhibitory postsynaptic specializations, or they can be inserted extrasynaptically (on the cell membrane outside the synapse). As shown in exhibit 4, in a normal setting, when a ligand binds to its complementary $GABA_A$ receptor, these receptors complete their inhibitory action, are endocytosed and degraded by the lysosome, and are recycled to complete their original purpose.

Exhibit 4
$GABA_A$ Receptor Endocytosis, Degradation, and Recycling



Sources: Jacob TC et al., *Nat Rev Neurosci* 2008 and William Blair & Company, L.L.C.

This homeostasis is integral to the proper functioning of the synapse, and $GABA_A$ receptor dysfunction in the recycling back to the synapse has been hypothesized to be the cause of several neurological diseases. $GABA_A$-receptor homeostasis dysfunction has been indicated in several neurological and psychiatric diseases, including epilepsy, schizophrenia, and Huntington's disease (Benarroch EE, *Neurology* 2007; Thompson-Vest MM et al, *Brain Res* 2003; Lewis DA, Gonzalez-Burgos G, *Nat Med* 2006). Epileptic episodes have been shown to be associated with both the up- and down-regulation of $GABA_A$ receptors (depending on the subunit) and the time point studied in the seizure state.

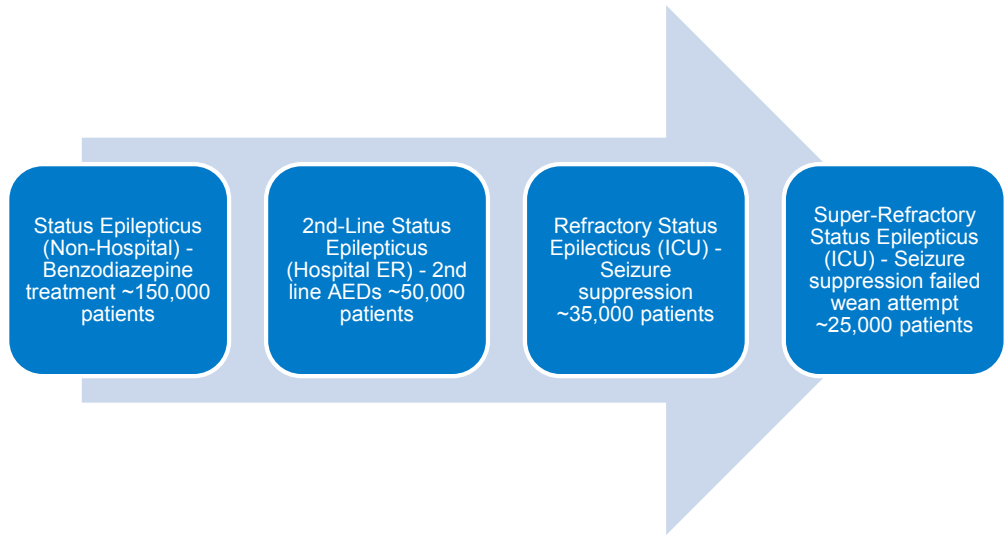
Studies have shown that decreases in synaptic $GABA_A$ receptors, as a result of increased endocytosis and reduced recycling, occur in SE (Naylor et al, *J Neurosci* 2005). In addition, the loss of these receptors from the cell surface, particularly considering the associated mechanism of $GABA_A$ synaptic receptor dysfunction, in SE patients likely leads to a reduced efficacy of front-line therapy of benzodiazepines for the treatment of seizures in later-stage patients.

Background on Status Epilepticus Disease

Seizures and seizure disorders are relatively common, with roughly 1 in 26 people in the United States likely to develop some sort of seizure disorder, and it is estimated that 10% of the total population have had a single unprovoked seizure during their lifetime. However, the occurrence of a single seizure does not lead to an epilepsy diagnosis, which normally requires at least two seizures to occur before diagnosis. As we progress along the continuum of seizure disorders, SE is more severe than general epilepsy and is diagnosed when a patient has a seizure lasting longer than five minutes. Refractory status epilepticus (RSE) is then diagnosed if seizure persists after second-line therapy and leads to the patient's admission to the ICU. The standard of care for patients with RSE is a medically induced coma, followed by what normally becomes several attempts to wean patients from the anesthetic agents. If patients do not respond to weaning attempts, they are maintained

in a medically induced coma and are diagnosed with SRSE. Although the exact prevalence is still unknown, SRSE is not an uncommon condition, and when it occurs, it is associated with a high percentage of mortality (30% to 50%) and morbidity. While SRSE may occur in patients with a history of epilepsy, there is a group of patients without a history of epilepsy in whom no identifiable etiology is found and who develop SE de novo. There is also a need in SE patients to continue to treat the underlying disease, which may be epilepsy, but may also be any number of causes of brain injury that precipitate the SE event.

Exhibit 5
Sage Therapeutics, Inc.
Status Epilepticus Market Potential and Current Standard of Care



Sources: Company reports

Current Therapeutic Strategies

When patients initially present with SE, they are treated with intravenous benzodiazepines, such as lorazepam, midazolam, and diazepam, as a front-line therapy. Unfortunately, a significant number of patients have a high tolerance for benzodiazepine therapy, possibly because of the degradation of the $GABA_A$ receptors after removal from the cell membrane and internalization. Second-line therapy includes anticonvulsants and sedative hypnotics, such as valproate, phenobarbital, and propofol. Beyond the use of these agents, there has been reported success in second and later lines of therapy of various polypharmacy combinations, which include benzodiazepines, anticonvulsants, hypothermia, a ketogenic diet, ketamine, and immune modulators (such as rituximab, cyclophosphamide, steroids, and IVIG). In exhibit 6, we show the recommendation (including dosage) for anesthetic usage in adult RSE and SRSE, published by Shorvon and Ferlisi in the journal *Brain* in 2011.

Exhibit 6
Recommendation for Anesthetic Use in Adult Refractory and Super-Refractory Status Epilepticus

Anesthetic	Dose	Recommendations
Thiopental/ pentobarbital	Thiopental: Loading dose: 2-3 mg/kg Maintenance dose: 3-5 mg/kg/g Pentobarbital Loading dose: 5-15 mg/kg Maintenance dose: 0.5-3 mg/kg/h	• First-line therapy in severe cases • Avoid in situations where pharmacokinetic interactions would be detrimental • Avoid hepatic disease, myasthenia gravis, porphyria, severe hemorrhage or burns, cardiovascular disease, adrenocortical insufficiency
Midazolam	Loading dose: 0.1-0.2 mg/kg Maintenance dose: 0.1-0.4 mg/kg/h	• First-line therapy in most cases. • Avoid in hepatic or renal disease, myasthenia gravis, porphyria
Propofol	Loading dose: 3-5 mg/kg Maintenance dose: 5-10 mg/kg/h	• First-line therapy in complex cases where ease of use and pharmacokinetic properties are important • Use where other drugs cause problematic hypertension • Avoid prolonged infusion (>48 hours), especially at high doses and in children • Caution with concurrent steroid or catecholamine therapy
Ketamine	Loading dose: 1-3 mg/kg Maintenance dose: up to 5 mg/kg/h	• Second-line therapy, especially where hypotension or cardiorespiratory depression is problematic

Source: Shorvon and Ferlisi, *Brain* 2012

Exhibit 7 shows the outcome of anesthetic therapy from a study published in 2012 by Shorvon and Ferlisi. In short, the authors of the study examined the published literature on treatment outcomes in about 1,168 patients and characterized the patients in one of six categories: 1) control: SE is completely controlled by the therapy; 2) no control ever achieved: therapy failed to control SE at all; 3) breakthrough seizures: recurrence on SE during treatment, despite initial control, which requires a change in therapy; 4) withdrawal seizures: recurrence of SE immediately after weaning of therapy, which requires a change in therapy; 5) therapy failure because of side effects: side effect profile required a change in therapy; and 6) death during therapy: all deaths, including both treatment-related and nontreatment-related. Current standard therapies in the published literature show control ranging from 64% to 78%, with a 74% rate in all cases examined and a range of 5% to 16% never achieving control of SE, with a 13% rate in all cases examined. The 26% of cases that end up in the adverse side effects, recurring SE, or death categories underline the significant unmet need in patients with RSE and SRSE. However, in our discussions with physicians, if SAGE-547 safety profiles were to continue to be impressive, physicians may move SAGE-547 to earlier lines of treatment, or Sage may look to develop its pipeline candidates for these earlier lines as well.

Exhibit 7
Overall Outcome of Anesthetic Therapy

Outcome	Thiopental/ pentobarbital (n=192)	Midazolam (n=585)	Propofol (n=143)
Control	64%	78%	68%
No control ever achieved	5%	16%	11%
Breakthrough seizures	0%	3%	1%
Withdrawal seizures	9%	<1%	6%
Therapy failure because of side effects	3%	<1%	6%
Death during therapy	19%	2%	8%

Source: Shorvon et al., *Brain* 2011

In exhibit 8, we show a suggested approach to therapy in RSE. It should be noted that morbidity rises with more extensive drug regimens, and rapid withdrawal of antiepileptic drugs can exacerbate the likelihood of recurring seizures. When RSE has been diagnosed, it also means that benzodiazepine tolerance has occurred; therefore, the use of these drugs, while likely continuing in a polypharmacy regimen, may not be contributing much incremental effect. As mentioned previously, beyond the

second line of therapy in RSE, physicians seem to focus on combinations that have shown some efficacy in published case reports; however, well-controlled larger trials are sparse in this late stage. Such therapies employed in RSE and SRSE include levetiracetam, topiramate, and lacosamide, with modulations such as hypothermia, magnesium infusion, and a ketogenic diet.

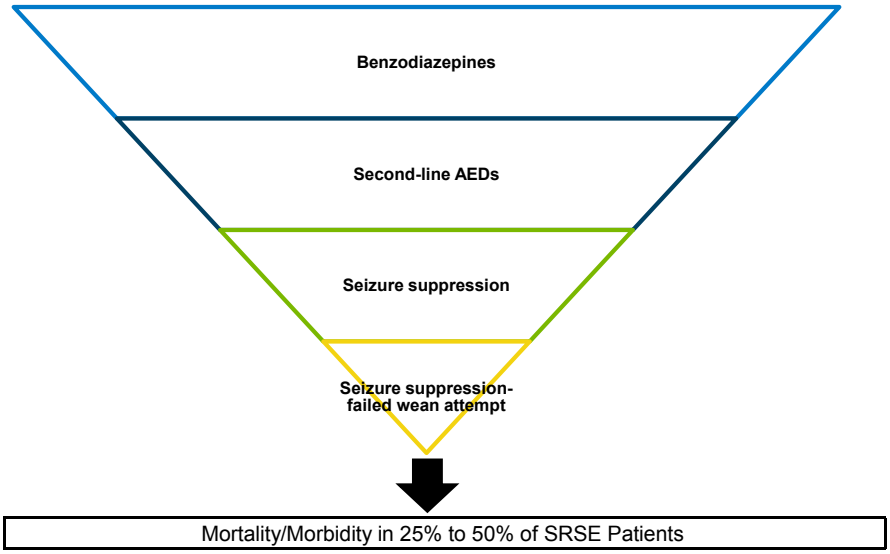
Exhibit 8
Suggested Approach to Antiepileptic Drug Therapy in Refractory Status Epilepticus

Choice of drug regimen depends on clinical context
Polytherapy with two antiepileptic drugs
High-dose regimens
Avoid frequent switching
Favor antiepileptic drugs with low interaction potential
Favor antiepileptic drugs with low predictable kinetic properties
Favor antiepileptic drugs without renal or hepatic toxicity
Avoid GABAergic antiepileptic drugs

Source: Shorvon and Ferlisi, *Brain* 2012

Exhibit 9 shows a therapeutic protocol for dealing with the various phases of SE. Patients who have progressed to SRSE are on several combinations of drugs and alternative therapies that have not significantly reduced the number or duration of seizures.

Exhibit 9
Treatment Hierarchy for Patients With SE, RSE, and SRSE



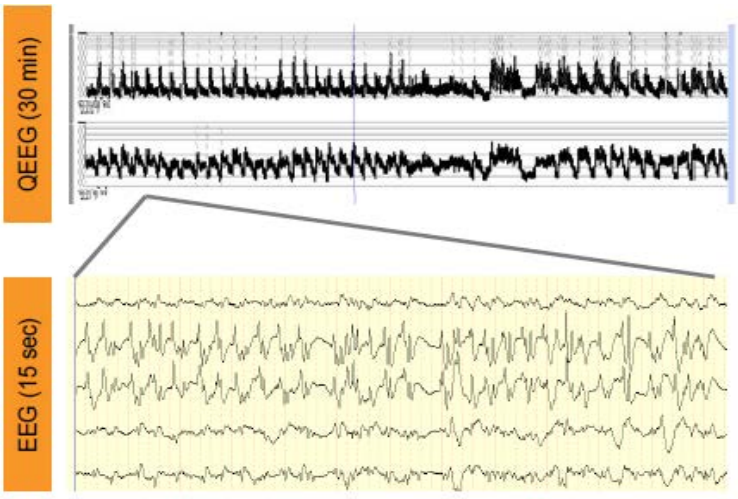
Sources: Company reports

SAGE-547 has been tested with all the previously mentioned therapies in a polypharmacy approach, which we believe follows from a lack of controlled trials in the setting. However, response rates continue to be impressive and our clinical consultants believe SAGE-547 is showing efficacy given the over 70% response in patients who are normally viewed as difficult to save.

Electroencephalogram (EEG) Measurements of Brain Activity

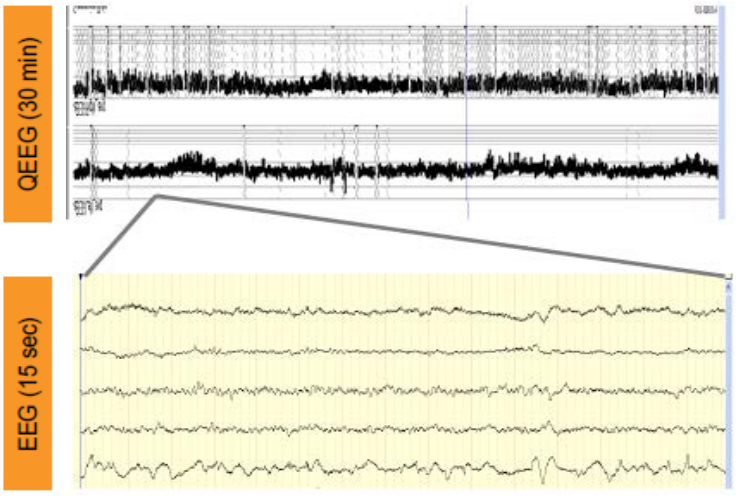
Status epilepticus is measured using an electroencephalogram (EEG), a test commonly used to detect the electrical activity of the brain. An EEG can be analyzed further using a quantitative EEG (qEEG) to provide brain mapping that can assist in the understanding of EEG measurements. Burst suppression is an EEG pattern that represents patients with inactivated brain states that usually occurs in coma or general anesthesia and is typical of SRSE patients. Exhibit 10 shows a sample patient EEG with burst suppression as a result of SRSE. The goal of treatment in status epilepticus patients is to wean them off general anesthesia therapy and not have a burst suppression EEG/qEEG profile, but to have a reduced amplitude EEG as illustrated in the example shown in exhibit 11.

Exhibit 10
Sample Burst Suppression EEG/qEEG



Source: Company reports

Exhibit 11
Sample EEG/qEEG of Patient With Burst Suppression Post-Therapy and Weaned Off General Anesthetic



Source: Company reports

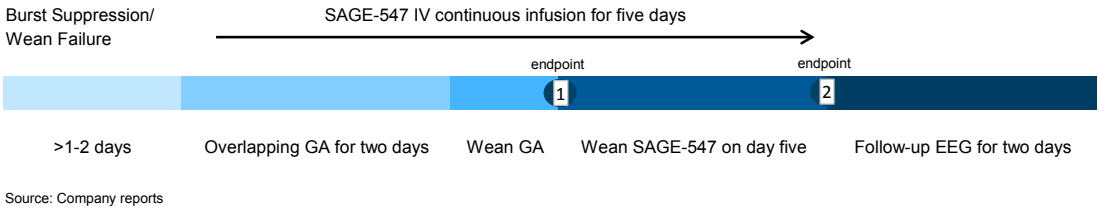
Pipeline Overview

Sage Therapeutics' development focus is on allosteric modulation, particularly small molecules that interact at alternative sites and affect neuronal signals. The company optimizes small molecule therapeutics to bind to either, or both, synaptic or extrasynaptic receptors. The company's lead product, SAGE-547, has binding affinity for both the $GABA_A$ α1 and α4 receptors, whereas benzodiazepines primarily target the α1 receptor. In preclinical studies, SAGE-547 showed increased efficacy compared with diazepam in a pilocarpine-induced rat model. The company is using its allosteric modulation platform to develop pipeline candidates with enhanced selection for $GABA_A$ receptors for earlier forms of SE, as well as NMDA receptors to potentially address other CNS conditions.

SAGE-547 Data to Date Suggests Efficacy

In preclinical studies, SAGE-547 showed increased efficacy compared with diazepam in a pilocarpine-induced rat model. The company initiated its Phase I/II study of SAGE-547 in January 2014, after filing its IND status in late 2013. The Phase I/II trial was designed to assess safety, tolerability, and efficacy in adult patients who have failed weaning after two prior antiepileptic drugs. Exhibit 12 shows the study protocol for the Phase I/II study. Patients with SRSE, regardless of etiology, were enrolled if they were in SE for greater than 24 hours after being treated with first- and second-line agents, failed to control seizures after over 24 hours on a general anesthesia (GA), and failed to wean from a GA after over 24 hours. Intravenous (IV) delivery of SAGE-547 was continuously infused for five days with overlapping GA for two days. On day three, the GA was weaned, with the first efficacy endpoint (SE, as measured by EEG) measured at the end of day three. SAGE-547 was continued for days four and five, and after weaning, the secondary efficacy endpoint was tested (SE, as measured by EEG at end of day five) with a follow-up EEG for two days after therapy.

Exhibit 12
Sage Therapeutics, Inc.
Phase I/II Study Protocol for SAGE-547 in SRSE



Source: Company reports

Exhibit 13
Sage Therapeutics, Inc.
Primary and Secondary Endpoints in Phase I/II Trial

Data readout	Phase I/II
Wean off GA and SAGE-547, no SRSE, duration of effect ≥ 24 h (Phase III endpoint)	12/17 (71%)
Wean off GA prior to taper of SAGE-547, no SRSE (Phase II endpoint)	12/17 (71%)
Drug-related serious adverse event	0/20*

*65% overall SAE rate and 5 deaths in study due to underlying disorders; unrelated to SAGE-547

Source: Company reports

In exhibit 13, we highlight the results from the Phase I/II study with SAGE-547. The study was designed to examine activity, with the first endpoint being the key variable. From a clinical standpoint, the importance of therapy is maintenance off-drug, with the first step in that process being free of

SE episodes. The Phase I/II study was able to meet the Phase II endpoint of weaning off GA before tapering the five-day infusion of SAGE-547 with no recurrent SRSE in 71% of patients (12 of 17 evaluable patients for efficacy) as of the latest view of the data. In addition, the prospective Phase III endpoint of weaning of GA and SAGE-547 with no SRSE and duration of effect of greater than, or equal to, 24 hours was met in 71% of patients (12 of 17 evaluable patients for efficacy) as well. There were no drug-related serious adverse events (AEs) in any of the 20 total treated patients.

In the company's S-1, it detailed four patients who had been treated up to that point, as we show in exhibit 14. The patients were in the range of 14 to 65 years of age, with each patient successfully weaning off his or her anesthetic while SAGE-547 was administered. In three of the patients, SAGE-547 was weaned without reinstating GA. Patient No. 1 was discharged to a rehabilitation facility; patient No. 3 remained hospitalized for other ongoing medical conditions; patient No. 2 experienced a recurrence of SE, requiring GA upon withdrawal of SAGE-547; and patient No. 4 had not finished the three-week follow-up period at the time of the S-1, but was recovering without an SE recurrence.

Exhibit 14
Sage Therapeutics, Inc.
Details on Four Cases From Phase I/II Study

Patient	#1	#2	#3	#4
Age/Sex	65/Male	14/Female	33/Female	36/Male
ICU Duration	12 days	11 days	21 days	4 days
Failed One or More Weaning Attempts	Yes	Yes	Yes	Yes
Etiology	Subdural Hematoma	Landau-Kleffner Syndrome	HIV / Toxoplasmosis	Seizure Disorder/ Pneumonia
Drug-Related Serious Adverse Event	None	None	None	None
Steady-State Plasma Levels >80 nM	Yes	Yes	Yes	Data pending
Key Efficacy Endpoint Met?	Yes	Yes	Yes	Yes

Source: Sage Therapeutics, Inc. S-1

Emergency-Use IND Status Reaffirms Need

In exhibit 15, we illustrate the results of the seven emergency-use IND cases. Seven out of nine patients (or 78%) were able to wean off the general anesthetic and SAGE-547 with no SRSE for greater than, or equal to, 24 hours (a projected Phase III endpoint). Similar to the Phase I/II trial, there were no drug-related serious AEs, with a younger age range than the clinical trial and a longer duration of SE (23 days versus 11 days).

Exhibit 15
Sage Therapeutics, Inc.
Primary and Secondary Endpoints in Emergency-Use Cases

Data Readout	Emergency Use
Wean off GA and SAGE-547, no SRSE, duration of effect ≥ 24 h (Phase III endpoint)	7/9 (78%)
Wean off GA prior to taper of SAGE-547, no SRSE (Phase II endpoint)	NA
Drug-related serious adverse event	0/9

Source: Company reports

Sage recently announced updated data from its ongoing emergency-use experience. It detailed nine of the cases in which an emergency use of SAGE-547 was used. In each of the nine cases, the treating physician applied for the emergency-use IND status with local institutional review board approval and proxy informed consent from the patient's next of kin. The cases arose from a variety of underlying etiologies, with patients ranging from 17 months to 28 years old. SAGE-547 was administered after multiple attempts to wean the patients from their medically induced comas

were unsuccessful. Exhibit 16 shows specific information from the first six patients disclosed in the company's S-1. Information included their ages/sexes, ICU duration of stay, etiology, drug-related severe AEs, and whether the SRSE was resolved. Patients were treated with a similar steady-state dose to the Phase I/II protocol.

Exhibit 16
Sage Therapeutics, Inc.
Emergency-Use Cases With SAGE-547

Patient	#1	#2	#3	#4	#5	#6
Age/Sex	23/Male	11/Female	28/Male	2/Female	17 Months/Male	14/Female
ICU Duration	>90 days	>60 days	>60 days	>30 days	>30 days	>30 days
Failed Multiple Weaning Attempts	Yes	Yes	Yes	Yes	Yes	Yes
Etiology	Unknown	Autoimmune (Anti-Thyroid/ Anti-GAD)	Unknown	Presumed Metabolic Disorder	Presumed Metabolic Disorder	Progressive Myoclonic Epileptic Encephalopathy
Drug-Related SAEs	None	None	None	None	None	None
Steady-State Plasma Levels > 80 nM	Yes	Yes	Yes	Yes	No	Yes
SE Resolved	Yes	Yes	Yes	Yes	No	Yes
Time From Discontinuation of SAGE-547 to Resolution of SRSE	Concurrent	Concurrent	3 days	Concurrent	N/A	3 days

Source: SAGE Therapeutics, Inc. S-1

In patient's no. 1, no. 2, and no. 4, resolution of SRSE occurred during the course of SAGE-547 treatment. Patient no. 1 was a 23-year-old male who had been previously treated with about 20 standard and alternative treatment regimens before SAGE-547, including lacosamide, phenobarbital, clonazepam, levetiracetam, bromides, and a ketogenic diet. Following SAGE-547 treatment, patient No. 1 had EEG normalization over the next 48-72 hours and successfully weaned from his medically induced coma. Patient no. 2 was an 11-year-old female who had been treated with various treatment regimens, including phenobarbital, valproate, phenytoin, fosphenytoin, topiramate, lacosamide, levetiracetam, and a ketogenic diet, and in combination with other drugs targeting the presumed underlying autoimmune etiology. On the fifth day of SAGE-547 therapy, phenobarbital was weaned, with the seizure burden significantly reduced. One week following SAGE-547 therapy, the patient was awake. Patient No. 4 was a two-year-old female who received initial therapy of levetiracetam and phenobarbital, as well as pyridoxine, methylprednisolone, benzodiazepine, propofol, and midazolam. Within 24 hours of SAGE-547 therapy, the patient successfully tapered off midazolam and pentobarbital and was no longer in SE after therapy.

In patient No. 3 and patient No. 6, SRSE resolution occurred three days after SAGE-547 treatment was discontinued. Patent No. 3 was a 28-year-old male who was treated with phenytoin, lacosamide, valproate, pregabalin, pyridoxine, magnesium, IV immunoglobulin (IVIG), and steroids. Over the SAGE-547 infusion period, EEG activity improved, and seizures were controlled by a combination of oral anti-seizure medications. Patient No. 6 was a 14-year-old female who was treated with IV midazolam, ethosuximide, levetiracetam, clobazam, and a ketogenic diet. The patient had several failed midazolam weans. After 24 hours of SAGE-547 therapy, the patient was successfully tapered off midazolam, pentobarbital was reduced, and the patient was no longer in SE after therapy.

Patient No. 5 did not resolve his SRSE with SAGE-547 treatment. Patient No. 5 was a 17-month-old male with seizure that continued despite front-line therapy with midazolam, phenobarbital, levetiracetam, lorazepam, and a maintenance dose of levetiracetam 50 mg/kg twice a day. Additional therapy as the seizures continued included pentobarbital, Solu-Medrol 30 mg/kg/day for five days, carnitine, coenzyme Q10, and riboflavin. After SAGE-547 therapy began, midazolam wean was attempted, but the patient experienced a recurrence of seizures.

In exhibit 17, we examine the combined data to date for patients treated with SAGE-547 for SRSE that had evaluable efficacy data, which sums to 26 patients, 19 (or 73%) of whom have met the endpoint of the Phase III trial of weaning of general anesthetic and SAGE-547 with no SRSE of greater than or equal to 24 hours. In addition, it should be noted that in all the emergency-use cases, as well as the Phase I/II study population, there were no drug-related serious AEs and the estimated mean duration of SE prior to therapy was about 23 days. The clean drug-associated safety profile in a patient population with normally dire outcomes combined with efficacy in both clinical trials and emergency cases gives us confidence that SAGE-547 has a high probability of eventual approval.

Exhibit 17
Sage Therapeutics, Inc.
Combined Results of SRSE Patients Treated With SAGE-547

Data Readout	Phase I/II + Emergency Use
Wean off GA and SAGE-547, no SRSE, duration of effect ≥ 24 h (Phase III endpoint)	73% (19/26)
Drug-related serious adverse event	0/29
Mean SAGE-547 exposure	200 nM
Mean duration of SE before SAGE-547	23 days (estimated)
Total patients (male/female)	30 (18/12)
Mean age (range)	39.4

Source: Company reports

Pediatric Study Continues to Suggest Efficacy of SAGE-547

Following initial efficacy results coming out of the Phase I/II study, a protocol amendment to treat pediatric patients greater than, or equal to, two years old was approved for SAGE-547. Early results from the expansion were published in late 2014 by Broomall et al in the *Annals of Neurology,* which examined the use of SAGE-547 in two pediatric SRSE cases. Like the initial results, both cases continue to suggest efficacy of SAGE-547 in heavily pretreated patients.

The first case was an 11-year-old girl who was treated with six days of IV methylprednisolone, plasmapheresis, IVIG, and rituximab. Seizures were subsequently treated with multiple IV antiseizure agents such as pentobarbital, propofol, phenytoin, and levetiracetam. Other therapies included magnesium infusion, mild hypothermia, ketamine, repeated immunotherapy with IVIG, steroids, cyclophosphamide, and rituximab. Multiple attempts to wean the patient off pentobarbital resulted in seizure recurrence. SAGE-547 was infused over five days, and the patient was weaned off pentobarbital with no serious drug-related AEs. SE did not recur after the infusion, and over the remainder of hospitalization, the patient had only one to two intermittent seizures, which were self-limited or responded to midazolam. The patient regained her ability to walk, and according to the study authors, she is continuing to show cognitive improvement by reading, doing arithmetic, and playing the piano.

The second case detailed in the paper is of a two-year-old girl who was treated with IV levetiracetam, phenobarbital, midazolam, and propofol. Two attempts to wean off midazolam during pentobarbital treatment resulted in seizure recurrence. The goal of SAGE-547 therapy was to wean the patient from pentobarbital and midazolam, with the secondary effects of discontinuing vasopressor support and restoring bowel function. SAGE-547 was infused for five days, and midazolam and pentobarbital were weaned. After the end of the SAGE-547 infusion, the patient experienced a seizure that was treated with a low dose of pentobarbital. The patient achieved the primary and secondary endpoints and was transferred to inpatient rehabilitation, where she regained the ability to walk and speak.

We believe that this significant improvement in two pediatric case studies highlights the potential of SAGE-547 to treat a life-threatening and serious unmet medical need. At present, SAGE-547 has received an orphan indication for SRSE and fast-track status by the FDA. Management believes that the potential size of a pivotal program will be on a scale of 100-200 patients, with the goal of achieving 50% efficacy in the primary endpoint. However, these numbers could be reduced, based on guidance received at the end–of–Phase II meeting. The company is looking to expedite the pivotal program and begin a double-blind, two-arm study comparing SAGE-547 with the best alternative therapy in 2015, if given permission by the FDA. Given the efficacy of SAGE-547 to date, we would expect the study to have a relatively high probability of success, and we have assumed a 75% chance of success in our NPV calculation.

Pivotal Study Initiation Will Be a Major Event

Sage management has not publicly commented on the FDA guidance for the company's pivotal study other than the company's intention on a pivotal trial initiation around midyear. Management is hoping for the FDA to sign off on a two-arm pivotal trial of 100-150 patients. Efficacy will be assessed at five days following dosing of SAGE-547, with a resolution of their SSRE and freedom from seizures at 48 hours. We believe that given the mixed etiologies leading to SRSE, polypharmacy in the indication, and no solid randomized trials, it would benefit the downstream marketing of SAGE-547 and the pricing potential of SAGE-547 for the company to show clear efficacy in a well-controlled trial. We also note that while none of the 20 patients treated to date exhibit drug-related serious AEs, there was an overall rate of 65% serious AEs in patients treated with SAGE-547. The inclusion of a comparator arm should reduce the marketing risk associated with all AEs being included on a potential label of SAGE-547 if a single-arm trial comprised the pivotal data set. Lastly, we believe that a two-arm pivotal trial would not change the timeline for an interim or final readout in comparison to a single-arm trial; therefore, having an improved label is even more beneficial for the company without sacrificing time.

SAGE-547 may potentially be granted a breakthrough therapy designation after its end–of–Phase II meeting with the FDA, given the high unmet medical need of SRSE patients and the efficacy to date. However, after SAGE-547 has already received fast-track designation, an expedited path through the FDA is likely with or without the breakthrough designation. However, we believe the breakthrough designation would further validate what we believe are impressive results to date.

In the appendix, we list the similarities and differences in the expedited review process for the FDA. A breakthrough therapy designation is for a drug that treats serious or life-threatening conditions, with preliminary clinical evidence indicating that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies. Fast-track designation is for a drug that treats serious or life-threatening conditions with nonclinical or clinical data demonstrating the potential for the drug to address the unmet medical needs for those conditions. When SAGE-547 received fast-track status (reported by the company on July 22, 2014), there was data available on only four patients in the Phase I/II clinical trial. With 17 patients treated in the Phase I/II and an additional 9 emergency-use INDs worth of data to present, we believe there is a high probability that the FDA will give SAGE-547 a breakthrough therapy designation, thereby expediting the approval timeline.

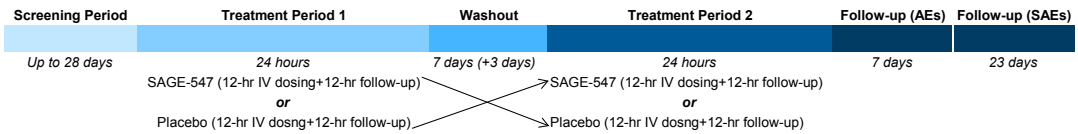
Not Just a One-Trick Pony; Pipeline Should Expand Opportunity

Moving beyond RSE and SRSE, Sage is also testing SAGE-547 for less severe essential tremor patients and women with severe postpartum depression (PPD). Essential tremor is a disorder in which rhythmic shaking can occur in almost any part of the patient's body, although it most often occurs in the hands. Essential tremor normally will worsen over time, and while it is not a life-threatening disease, it complicates many normal tasks and may lessen a patient's quality of life, especially in severe cases. Essential tremor is inherited by an autosomal-dominant pattern; it has shown a prevalence of 4% in people less than 40 years old and roughly 14% in people 65 years or older (Dogu et al, *Neurology* 2003, Moghal et al, *Neuroepidemiology* 1994). Studies have shown that essential tremor could be associated with $GABA_A$ receptor dysfunction and an increased availability of benzodiazepine receptors (Boecker et al., *Journal of Nuclear Medicine* 2010).

Based on this mechanism, the company has enrolled a Phase IIa study to establish this proof-of-concept in the clinical setting. As shown in exhibit 18, the study design consists of a 12-hour intravenous dosing treatment period and a 12-hour follow-up with SAGE-547, with a matched placebo group, followed by a washout period and a switch of therapies (i.e., the SAGE-547 group would be treated with placebo and the placebo group treated with SAGE-547). Follow-up over the course of 30 days would then occur, with the first seven days for AEs and the next 23 days for serious adverse events (SAEs). The proof-of-concept study will be used to guide the development of an oral compound for chronic use, as the intravenous administration of SAGE-547, while suited to the SRSE setting, would not be commercially viable for essential tremor.

The essential tremor market is significant. It is estimated that a mean of 7.01 million people in the United States, or 2.2% of the U.S. population, have essential tremor, with about 1.5 million of that population having moderate to severe essential tremor (Louis ED and Ottman R, *Tremor Other Hyperkinet Mov* 2014). There are currently only two first-line medications, primidone and propranolol, that have been shown to be effective in about 50% of patients, but use of these agents was also associated with AEs, such as nausea, ataxia, and sedation for primidone (Deuschl et al, *Lancet Neurol 2011) and hypotension, bradycardia, and depression in the case of propranolol (Zesiewicz et al, Curr Treat Options Neurol 2013).*

Exhibit 18
Sage Therapeutics, Inc.
Phase IIa Study Design of SAGE-547 in Essential Tremor



Source: Company reports

In mid-January, the company also announced the initiation of a Phase IIa exploratory trial of SAGE-547 in women with PPD to examine safety, tolerability, pharmacokinetics, and efficacy. It is estimated that 1.0% to 6.8% of women experience severe PPD in the first year following the birth of a child, with a peak of six weeks after child birth (O'Hara and Wisner, *Best Pract Res Clin Obstet Gynaecol* 2014), making it the most underdiagnosed obstetric complication in the United States (Earls MF, *Pediatrics* 2010). The trial is an open-label study of SAGE-547 as an adjunctive therapy to current approaches with an expected enrollment of 10 women with PPD who have experienced a major episode within four weeks following delivery. SAGE-547 will be delivered for 48 hours intravenously, and patients will then be monitored for up to 30 days following treatment. The primary efficacy endpoint is measured by two scales: the Hamilton Rating Scale for Depression (HAM-D) and the Clinical Global Impression Improvement Scale (CGI-I).

In addition to SAGE-547, the company is using its allosteric modulation platform technology to develop a therapy called SAGE-217 to treat earlier forms of SE (such as RSE). SAGE-217 is considered by the company to be a second-generation $GABA_A$ receptor ligand, which may be suitable for oral dosing with higher binding efficiency (Emax in α1 receptor—SAGE-547: 342%; SAGE-217: 641%; Emax in α4 receptor—SAGE-547: 418%; SAGE-217: 531%). In animal models, SAGE-217 has been shown to have improved potency, optimized clearance as a result of an increased half-life, and minimal off-target effects. The other pipeline product being tested by the company is SAGE-689 as an IV-adjunctive therapy in second-line SE. In animal models, SAGE-689 has shown to be a potentially safer alternative to propofol, and may be used before placing a patient in a medically induced coma. Both compounds are currently in their IND-enabling studies, and management expects the compounds to be in Phase I trials in normal adults for pharmacokinetics, safety, and tolerability by late 2015. It should be noted that the potential indications for SAGE-217 and SAGE-687 do not overlap with SAGE-547. SRSE is a disorder in which an IV delivery is beneficial due to a shorter half-life and the ability to control dose acutely considering the cocktail of other therapies these patients are being dosed with. The more likely use for Sage's pipeline products are for indications that require a longer-half life with a more targeted profile to reduce off-target effects that may come along with increased duration of bioavailability.

Lastly, the company is also developing its platform to target NMDA receptors, with the goal of identifying patient populations with NMDA dysfunctions for potential treatment. Overall, the company expects to conduct preclinical studies with its pipeline products to treat other seizure disorders, such as Dravet syndrome, Rett syndrome, and disorders associated with anxiety and depression. We believe that the company has developed a platform by which it can target alternative mechanisms that may provide an advantage over standard-of-care therapies for rare CNS disorders.

Competitive Landscape

We believe that Sage Therapeutics is developing a stand-alone therapy in SAGE-547 for SRSE and that its clinical program and meetings with the FDA are ground-breaking in the field. However, with its overall goal to address several other CNS disorders with its pipeline products and platform technology, it has entered a competitive landscape with several other biopharmaceutical companies whose progress should also be monitored. Importantly, the below programs should not be competitive with SAGE-547 in the SRSE setting however they will likely be competitive to the company's follow-on programs in rare epilepsies.

Marinus Pharmaceuticals, Inc.
Marinus Pharmaceuticals is another developmental-stage biopharmaceutical company that is developing CNS therapies. Its primary candidate, ganaxolone, is also a synthetic analog of allopregnanolone (one methyl group added) being studied for adjunctive treatment of focal onset epileptic seizures, PCDH19 female pediatric epilepsy, and behaviors in Fragile X syndrome. Being an analog of allopregnanolone, ganaxolone has a mechanism of action similar to the SAGE compounds by targeting synaptic and extrasynaptic $GABA_A$ receptors.

Ganaxolone has completed a Phase II study in the adjunctive treatment of drug-resistant adult focal onset seizures with statistically significant reduction in seizures from baseline versus placebo (as shown in exhibit 19). The company is undergoing a Phase III trial in a randomized two-cohort study; top-line results are expected by the second half of 2015. We believe that this study, if positive, could be a positive for Sage Therapeutics. In a presentation for the Twelfth Eilat Conference on New Antiepileptic Drugs (EILAT XII), Sage's chief scientific officer, Al Robichaud, Ph.D., presented on differences between SAGE-547, SAGE-217, and ganaxolone in animal acute seizure models and showed three fold better potency over ganaxolone for SAGE-547 and a six times improvement with SAGE-217 (SAGE-217 EC50 = 188 nM; SAGE-547 EC50 = 452 nM; Ganaxolone EC50 = 1270 nM). As

shown in exhibit 20, Dr. Robichaud also made comparisons between the three compounds across other acute seizure models, SE models, and epilepsy models, which show superior results with SAGE-217 and SAGE-547 over ganaxolone.

Exhibit 19
Ganaxolone Phase II Primary Endpoint (% Seizure Reduction Over Baseline (ITT))

	Ganaxolone N=98	Placebo N=48	Ganaxolone-Placebo Difference
Mean (SD)	-17.6% (48.9)	-+2.0% (63.2)	19.6%; P=0.014
Median	-26.0%	-10.2%	15.7%

Source: Marinus Pharmaceuticals, Inc. reports

Exhibit 20
Comparison of Efficacy in Status Epilepticus (SE) Animal Models

SAGE-217	SAGE-547	Ganaxolone
SAGE-217 terminates SE in 80% of rats when administered 15 minutes after SE onset	Allopregnanolone terminates SE in all rats when administered 15 minutes after SE onset	Ganaxolone terminates SE in 60% of rats when administered 15 minutes after SE onset
	Allopregnanolone also terminates RSE in all rats when administered 60 minutes after SE onset	Ganaxolone did not terminate pharmaco-resistant SE (RSE) in any rat when administered 60 minutes after SE onset

Source: Robichaud AJ, EILAT XII

GW Pharmaceuticals plc

GW Pharmaceuticals' primary focus is the development of prescription cannabinoid medicines. The company has two pipeline products to treat epilepsy disorders, Epidiolex and GWP42006. Epidiolex received orphan and fast-track designations from the FDA to treat Dravet syndrome. Dravet syndrome is a rare genetic epileptic encephalopathy (primarily associated with a mutation in SCN1A) that begins in the first year of life and results in prolonged seizure events. According to the Dravet Syndrome Foundation, the incidence of the disease is estimated to be between 1 in 20,000 and 1 in 40,000 infants. GW Pharmaceuticals has an ongoing Phase II/III trial that commenced in October 2014 and has treated 58 patients to date with at least 12 weeks of continuous exposure. Its data has shown a median overall reduction in total seizure frequency between 36% and 51%, with 95% of patients remaining on therapy. Dravet syndrome was considered by Sage to be a potential indication for future research on SAGE-547. In addition to Dravet syndrome, Epidiolex has also received orphan indication for Lennox–Gastaut syndrome (LGS). According to the LGS Foundation, the disease is rare and severe form of childhood-onset epilepsy, characterized by multiple and frequent seizures that occur primarily between ages two and six. We consider GW Pharmaceuticals to be a good comparison company to Sage Therapeutics as it progresses its clinical program.

Zogenix, Inc.

In October 2014, Zogenix acquired Brabant Pharma, which has a primary candidate for Dravet syndrome called Brabafen, a low-dose fenfluramine with orphan indication in the United States and Europe. Zogenix expects to initiate two pivotal Phase III clinical trials in second quarter 2015, with 40 to 60 Dravet syndrome patients per study and top-line results expected in the first half of 2016. Patients under a standard-of-care treatment (such as a combination of valproate, clonazepam, or topiramate, and a ketogenic diet) will be randomized 1:1 to standard-of-care plus placebo or standard-of-care plus Brabafen. In concert with the pivotal Phase III program, the company is also developing a Risk Evaluation Mitigation Strategy (REMS) ahead of its potential NDA submission because of some of

the known cardiovascular safety risk factors associated with fenfluramine use. Results from a longitudinal analysis of up to 26 years of clinical data in a study with 15 children and adults with Dravet syndrome who were treated with low-dose fenfluramine as an add-on therapy for an average of 12.4 years showed that 67% of patients were seizure-free at the latest assessment. The average seizure-free period was 5.5 years, and 87% of patients had greater than 75% reduction in seizure frequency at the last assessment. We will continue to monitor the development of Brabafen in Dravet syndrome and any other indications the company pursues in the orphan epileptic disease space.

Breakthrough Therapy

According to the Friends of Cancer Research, as of December 3, 2014, the FDA had given approval to 15 drugs that have received the breakthrough therapy designation. In addition, the FDA lists 97 total requests for breakthrough therapy designation in the Center for Drug Evaluation and Research (CDER), with 31 requests granted, 51 requests denied, and 99% of actions taken within 60 days of receipt of the request. If a breakthrough therapy designation is granted, the FDA and the sponsor work closely together to determine an efficient path to approval, with the FDA expediting the development and review of the drug.

In exhibit 21, we show the drugs with the breakthrough therapy designation approved by the CDER, the applicant, and NDA submission/approval dates. According to the date at which the FDA accepts the NDA submission from the company, the average time for breakthrough therapy product approval is five to six months, with relatively new processes becoming more efficient and the time from NDA submission to approval being as fast as four months, in the case of Novartis's Zykadia. In the appendix, we present an overview of the FDA's expedited programs; the standard time from NDA submission to PDUFA date is 10 months. The accelerated approval pathway shortens the time from NDA submission to PDUFA date to six months, and the breakthrough therapy designation, with a similar timeline to accelerated approval, also features intensive guidance from the FDA of the regulatory submissions with a rolling review.

We believe a breakthrough therapy indication for SAGE-547 would provide significant upside to the company's value, with a potentially reduced sample size requirement for its pivotal clinical study and potential NDA submission. In addition, we believe that there is a probability that SAGE-547 will receive this designation, as a result of the number of emergency-use IND statuses already granted by the FDA and the significant improvement shown over current standard-of-care therapies in the SRSE population.

Exhibit 21
Calendar 2014 CDER Breakthrough Therapy Approvals

Applicant	Submission Type and Number	Proprietary Name	Established Name	NDA Accepted Date	Breakthrough Therapy Designation Date	NDA Approval Date	NDA Accepted to Approval Time
Vertex Pharmaceuticals	Supplement-4	Kalydeco	Ivacaftor	September 27 2013	January 30 2014	February 21 2014	5 months
GlaxoSmithKline	Supplement-60	Arzerra	Ofatumumab	September 2013	September 19 2013	April 17 2014	8 months
Novartis	Original-1	Zykadia	Ceritinib	January 2014	March 15 2013	April 29 2014	4 months
Gilead	Original-1	Zydelig	Idelalisib	January 13 2014	December 13 2013	July 23 2014	6 months
Pharmacyclics	Supplement-1	Imbruvica	Ibrutinib	April 7 2014	NA	July 28 2014	4 months*
GlaxoSmithKline	Supplement-12	Promacta	Eltrombopag	February 27 2014	February 3 2014	August 26 2014	6 months
Merck Sharp & Dohme Corp	Original-1	Keytruda	Pembrolizumab	February 27 2014	August 7 2014	September 04 2014	6 months
Gilead	Original-1	Harvoni	Ledpasvir/Sofosbuvir	February 10 2014	August 19 2014	October 10 2014	8 months
Boehringer Ingelheim	Original-1	Ofev	Nintedanib	May 2 2014	August 26 2014	October 15 2014	5.5 months
Intermune/Roche	Original-1	Esbriet	Pirfenidone	May 27 2014**	July 17 2014	October 15 2014	4.5 months
Average Time From Submission to Approval Under Breakthrough Therapy Designation in 2014: ~5-6 months							

*Supplemental NDA
**NDA resubmitted after initial CRL
Sources: FDA Web site and company reports

Valuation and Financial Overview

Valuation

Shares of Sage Therapeutics have traded up more than 180% since the company's shares were priced at $18, the upper end of its range of $17 to $18, during the IPO process in July 2014. The S&P 500 rose 11%, the Nasdaq Biotechnology Index increased 34%, and the Russell 2000 rose 3.5% during 2014. We continue to believe shares of Sage hold a strong risk/reward profile, given the potential for significant profitability pending successful development of SAGE-547 and the company's disclosed pipeline products that look to build off the company's proprietary platform. In addition, the fast-track designation, orphan indication, and several emergency-use IND statuses received from the FDA offer reduced development risk compared with many small-cap, development-stage specialty pharmaceutical companies, in our view.

We are establishing a price target of $75, based on a net present value of the company's lead development program for SAGE-547 in the U.S. and ex-U.S. markets. In this calculation, we assume a launch of SAGE-547 in mid- to late 2017; however, this timing will be influenced by the company's enrollment of its pivotal study, which should be initiated near midyear. We believe that peak-year sales could be about $1.1 billion domestically, assuming a $50,000 cost per year for patients in the United States and a steep ramp-up to roughly 80% penetration of the patient population at the time of peak U.S. sales. Internationally, we assume 60% penetration at peak, with approval in mid- to late 2018 for peak sales of $289 million, assuming the company does not pursue a licensing strategy (which would change our estimates). Risks to this timeline are primarily clinical and regulatory, such as the possibility of the efficacy of SAGE-547 declining in future emergency-use IND statuses or clinical trials. We project a complete Phase III clinical program to begin in 2015 for SAGE-547 and a full review process, assuming positive clinical outcomes. Our current NPV does not include SAGE-217 or SAGE-689, which we believe are too early in the development process to assign any value to. Our full model with additional details is available from a William Blair salesperson.

Exhibit 22
Sage Therapeutics, Inc.
Risk-Adjusted Sum-of-the-Parts Valuation

Program	Peak Sales	Discount Rate	Probability of Success	Value	Value Per Share
SAGE-547 in SRSE (U.S./ex-U.S.)	$1.95B	11%	80%	$1,803,346	$77.18
Cash Per Share				$127,766	$5.47
Discounted value of future net loss				($169,290)	($7.25)
Sum-of-the-parts NPV Valuation				$1,761,821	$75.40

Source: William Blair & Company L.L.C. estimates

In exhibit 23, we provide the enterprise values (EVs) of several public biopharmaceutical companies, many of which are developing products with a small number of patients tested to date, albeit with a potential game-changing therapy. The average EV for Sage's biopharmaceutical peer group is roughly 1.5 times higher than the roughly $984 million EV of Sage, which we believe suggests significant room for upside from current levels if the company were to receive favorable guidance from its end–of–Phase II meeting with the FDA.

Exhibit 23
Public Company Comps

Company	Ticker	Rating	Price Target	Price	Market Cap (in millions)	Consensus EPS Estimates			Enterprise Value (in millions)
						2014A	2015E	2016E	
Receptos, Inc.	RCPT	Outperform	N/A	$145.74	$4,597	($4.63)	($5.86)	($5.54)	$3,925
bluebird bio, Inc.	BLUE	Not Rated	N/A	$120.46	$3,923	($1.83)	($2.61)	($3.06)	$3,717
Kite Pharma, Inc.	KITE	Not Rated	N/A	$63.52	$2,657	($0.99)	($1.62)	($0.70)	$2,635
Auspex Pharmaceuticals, Inc.	ASPX	Outperform	$105.00	$82.75	$2,633	($2.68)	($3.22)	($1.96)	$2,614
Ultragenyx Pharmaceutical, Inc.	RARE	Not Rated	N/A	$60.92	$2,123	($14.87)	($2.10)	($2.25)	$2,069
GW Pharmaceuticals plc	GWPH	Not Rated	N/A	$97.20	$1,917	($1.31)	($3.36)	($4.11)	$1,653
Sage Therapeutics, Inc.	**SAGE**	**Outperform**	**$75.00**	**$50.47**	**$1,293**	**($1.67)**	**($2.18)**	**($2.76)**	**$1,163**
Marinus Pharmaceuticals	OTIC	Not Rated	N/A	$38.50	$913	($5.46)	($2.81)	($2.92)	$877
Sarepta Therapeutics, Inc.	SRPT	Outperform	$34.00	$13.66	$564	($3.39)	($4.26)	($3.23)	$300
Mean									**$2,106**
Median									**$2,069**

Sources: FactSet and William Blair & Company, L.L.C. estimates

Income Statement

The performance of Sage Therapeutics' shares will largely be driven in the near term by the clinical development and regulatory guidance related to SAGE-547. We expect the company to be cash flow negative through fiscal 2017, under a conservative clinical timeline leading to approval of SAGE-547 in mid- to late 2017 in the United States. We believe the company will break into profitability during 2018, with a gross margin at 85%. Beyond fiscal 2017, we anticipate the company will be highly profitable, with earnings potentially exceeding $6.00 in 2019, based on our current estimates. We believe SG&A expenses will ramp up from about $9 million in fiscal 2014 to $25 million in fiscal 2017, as Sage launches SAGE-547 in the United States. We expect a significant ramp-up of R&D expenses from $22.2 million in fiscal 2014 to more than $40 million in fiscal 2017 as the company continues developing SAGE-547 in additional indications, such as essential tremor, and clinical pipeline candidates SAGE-217 and SAGE-689. The company seems dedicated to developing second- and third-generation compounds to treat earlier forms of SE, using its platform technology. Our income statement is shown in exhibit 24.

Balance Sheet and Cash Flow

We estimate that Sage held about $127.8 million in cash on its balance sheet as of the end of the fourth quarter, with capital raised from its $103.5 million IPO in July 2014 and a $38 million Series C crossover financing in March 2014. Use of proceeds from the offering includes mostly the clinical costs of taking the company's products through development and regulatory approval. Dating to 2012, Sage has accumulated net losses of about $52 million, while cash used in operating activities through the first three quarters of 2014 was about $21 million. We anticipate that Sage will use about $52 million in 2015; however, this spending will be heavily influenced by the speed of enrollment for the company's SAGE-547 pivotal trial in SRSE. Spending on the development of SAGE-217 and SAGE-687 may also accelerate during 2015, which may increase the company's cash usage.

Key Management

Sage Therapeutics has assembled a management team and board of directors with significant experience in the specialty pharmaceuticals industry. Chief Executive Officer Jeff Jonas has significant experience with clinical development in his roles at Shire Pharmaceuticals and Isis Pharmaceuticals. Early in his career, Dr. Jonas was involved in the development of alprazolam (Xanax) and has deep experience in therapies in CNS disorders. Dr. Steve Kanes, chief medical officer, and Dr. Robichaud, chief scientific officer, both come to Sage with experience in large pharmaceutical companies, again with experience in CNS and neuroscience drug development. We have included biographies of key executives below.

Jeff Jonas, M.D., chief executive officer. Dr. Jonas has been CEO of Sage Therapeutics since 2013. He previously served as the president of regenerative medicine and senior vice president of R&D, pharmaceuticals at Shire Pharmaceuticals. In addition, he has served as chief medical officer of Isis Pharmaceuticals and in various roles at Forest Laboratories and Upjohn Laboratories. Dr. Jonas was the chief resident in psychopharmacology at McLean Hospital and received his M.D. and completed a medical residency in psychiatry at Harvard Medical School. He received his B.A. from Amherst College.

Kimi Iguchi, CPA, chief financial officer. Ms. Iguchi has served as the chief financial officer since 2013. Ms. Iguchi previously served as the chief operating officer of Santhera Pharmaceuticals and in various finance roles for Cyberkinetics Neurotechnology Systems and Millennium Pharmaceuticals. She also worked for Biogen Idec and PricewaterhouseCoopers LLP. Ms. Iguchi received her M.B.A. from Northeastern University and her B.A. in chemistry from Drew University.

Steve Kanes, M.D., Ph.D., chief medical officer. Dr. Kanes has been the chief medical officer of Sage since 2013. Before his appointment at Sage, Dr. Kanes served in various roles at AstraZeneca, including chair of the neuroscience safety group, therapeutic area clinical director, medical science senior director, and other positions in the neuroscience discovery medicine group. Before his tenure at AstraZeneca, Dr. Kanes was a faculty member in the psychiatry department at the University of Pennsylvania. He received his Ph.D. and M.D. from the State University of New York at Stony Brook, completed his psychiatry residency at Yale, and completed his postdoctoral fellowship at the University of Pennsylvania. He also received his B.A. from the University of Pennsylvania.

Al Robichaud, Ph.D., chief scientific officer. Dr. Robichaud has served as the chief scientific officer for Sage Therapeutics since 2011. He was previously the vice president of chemistry and pharmacokinetic sciences at Lundbeck, Inc. From 2002 to 2010, he was the senior director and head of the neuroscience discovery chemistry department of Wyeth Research. Dr. Robichaud received his Ph.D. in organic chemistry from the University of California and completed his postdoctoral fellowship at Colorado State University. He received his B.S. in chemistry from Rensselaer Polytechnic Institute.

Conclusion

Sage Therapeutics is developing a therapy in SAGE-547 that has shown significant efficacy above the current available therapies to treat the rare CNS disorder of super-refractory status epilepticus, which affects about 25,000 patients in the United States. The company has tested 17 patients in a Phase I/II clinical trial; 71% of patients met the primary endpoint with no drug-related serious adverse events, and Sage has received nine emergency-use IND statuses, in which 78% of patients met the primary endpoint with no drug-related serious adverse events. SAGE-547 has already received orphan status and fast-track designations from the FDA. From the data produced to date and specific detail from several clinical cases, we believe that SAGE-547 represents a significant benefit for patients who have little to no therapeutic options and a high probability of mortality and morbidity. Furthermore, we believe that Sage is pioneering therapies in the rare CNS disease space and leveraging its neurosteroid platform to potentially treat earlier stages of status epilepticus with more targeted therapies. Therefore, we are initiating coverage of Sage Therapeutics with an Outperform rating and $75 price target.

Exhibit 24
Sage Therapeutics, Inc.
Projected Income Statement
($ in thousands, except EPS data)

	2012(A)	2013(A)	2014(A)	Q1(E)	Q2(E)	Q3(E)	Q4(E)	2015(E)	2016(E)	2017(E)	2018(E)	2019(E)
Product Revenue	-	-	-	-	-	-	-	-	0	57,795	167,548	433,588
SAGE-547	-	-	-	-	-	-	-	-	0	57,795	167,548	433,588
SAGE-687	-	-	-	-	-	-	-	-	-	-		
SAGE-217	-	-	-	-	-	-	-	-	-	-	-	-
Other Revenue		-	-	-	-	-	-	-	-	-		
Total Revenue	-	-	-	-	-	-	-	-	-	57,795.1	167,548.4	433,587.7
yr/yr growth		NM	NA	NA	NA	NA	NA	NA	NA	NA	189.9%	158.8%
q/q growth				NA	NA	NA	NA					
incremental rev q/q												
Cost of Goods Sold	-	-	0	0	0	-	-	-	-	11,559	33,510	86,718
Gross Profit	-	-	0	0	0	0	0	0	0	46,236	134,039	346,870
SG&A	2,402	3,922.0	9,710	4,000	5,000	6,000	6,000	21,000	24,570	28,256	38,144.9	49,588.4
Growth		63%	20%					116%	17%	15%	35%	30%
R&D	7,229	14,357.0	24,100	9,000	10,000	12,000	12,000	43,000	37,000	41,255	45,380.5	47,649.5
Growth		99%	68%	116%	128%	82%	34%	78%	12%	12%	10%	5%
Total Operating Expenses	9,631	18,279	33,810	13,000	15,000	18,000	18,000	64,000	61,570	69,511	83,525	97,238
Growth			85%	125%	142%	90%	46%	89%	-4%	13%	20%	16%
Operating Income	(9,631)	(18,279)	(33,810)	(13,000)	(15,000)	(18,000)	(18,000)	(64,000.0)	(61,570.0)	(23,274.4)	84,023	336,350
growth y/y (%)			85%	125%	142%	90%	46%	89%	-4%	-62%	-461%	300%
Depreciation and Amortization			33	13	13	13	13	50	100	100	100	100
EBITDA	(9,631)	(18,279)	(33,777)	(12,988)	(14,988)	(17,988)	(17,988)	(63,950)	(61,470)	(23,174)	84,123	336,450
Interest income (expense), net	-	1	8									
Other income (expense), net	(1.0)	(3.0)	(9)	500	500.0	500.0	500.0	2,000	2,000	2,000	2,000	2,000
Income Before Taxes	(9,632.0)	(18,281.0)	(33,811)	(12,500.0)	(14,500.0)	(17,500.0)	(17,500.0)	(60,000)	(59,570)	(21,274)	86,022.9	338,349.8
Income Tax Provision	-	-	-	-	-	-	-	-	-	(7,659)	30,968.26	121,805.92
Effective Tax Rate	0%	0%	0%	0.0%	0.0%	0.0%	0.0%	0%	0%	36%	36%	36%
Accretion of redeemable conv pref stock to redemp value	(4)	(7)	(2,294)									
Net Income (loss)	$ (9,636)	$ (18,288)	$ (36,105.0)	(12,500.0)	(14,500.0)	(17,499.9)	(17,500.0)	$ (59,999.9)	$ (59,569.9)	$ (13,615.6)	$ 55,054.7	$ 216,543.9
Net loss per share (fully diluted)	$ (8.62)	$ (12.26)	$ (1.67)	$ (0.63)	$ (0.72)	$ (0.87)	$ (0.87)	$ (3.09)	$ (2.95)	$ (0.60)	$ 2.22	$ 8.07
Basic and diluted weighted avg. shares of common out	1,118	1,492	21,574	19,901	20,001	20,101	20,201	20,051	20,826	22,826	24,826	26,826
Key Ratios (GAAP unless noted)												
Gross Margin	NM	NM	NM	NM	NM	NM	NM	NM	NM	80.0%	80.0%	80.0%
R&D (% Total Rev.)	NM	NM	NM	NM	NM	NM	NM	NM	NM	71.4%	27.1%	11.0%
SG&A (% Total Rev.)	NM	NM	NM	NM	NM	NM	NM	NM	NM	48.9%	22.8%	11.4%
Operating Margin	NM	NM	NM	NM	NM	NM	NM	NM	NM	-40.3%	50.1%	77.6%
Net Income Margin	NM	NM	NM	NM	NM	NM	NM	NM	NM	-23.6%	32.9%	49.9%
Revenue Growth												
Growth Yr/Yr	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	190%	159%
Growth Q/Q	NM			NM	NM	NM	NM					
SG&A Growth												
Growth Yr/Yr	NM	63%	148%	147%	177%	109%	76%	116%	17%	15%	35%	30%
Growth Q/Q	NM			17%	25%	20%	0%					
R&D Growth												
Growth Yr/Yr	NM	99%	68%	116%	128%	82%	34%	78%	-14%	12%	10%	5%
Growth Q/Q	NM			1%	11%	20%	0%					

Sources: Company reports and William Blair & Company, L.L.C. estimates

Exhibit 25
Sage Therapeutics, Inc.
Net Present Valuation of SAGE-547

SAGE-547 U.S. NPV Valuation	**2015**	**2016**	**2017**	**2018**	**2019**	**2020**	**2021**	**2022**	**2023**	**2024**	**2025**
Patients with Status Epilepticus	150,000	153,000	156,060	159,181	162,365	165,612	168,924	172,303	175,749	179,264	182,849
% of pts successfully treated with Benzodiazepenes	67%	67%	67%	67%	67%	67%	67%	67%	67%	67%	67%
Patients that may develop 2nd-line Status Epilepticus (SE)	50,100	51,102	52,124	53,167	54,230	55,314	56,421	57,549	58,700	59,874	61,072
% of patients successfully treated with 2nd line AEDs	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%
Patients that develop Refractory Status Epilepticus (RSE)	35,070	35,771	36,487	37,217	37,961	38,720	39,495	40,284	41,090	41,912	42,750
% of patients successfully treated with burst suppression	28%	28%	28%	28%	28%	28%	28%	28%	28%	28%	28%
Patients that develop Super Refractory Status Epilepticus (SRSE)	25,250	25,755	26,271	26,796	27,332	27,878	28,436	29,005	29,585	30,177	30,780
Cost per year ($)	$55,000	$55,000	$55,000	$56,650	$58,350	$60,100	$61,903	$63,760	$65,673	$67,643	$69,672
Gross to net adjustment	80%	80%	80%	80%	80%	80%	80%	80%	80%	80%	80%
% penetration of patients with SRSE	0%	0%	5%	10%	22%	40%	65%	65%	65%	65%	65%
SRSE Patients on SAGE-547	0	0	1,314	2,680	6,013	11,151	18,483	18,853	19,230	19,615	20,007
SAGE-547 U.S. Sales (SRSE)	$0	$0	$57,795	$151,799	$350,856	$670,199	$1,144,180	$1,202,075	$1,262,900	$1,326,803	$1,393,939
% penetration of U.S. patients with RSE	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
RSE Patients on SAGE-547	0	0	0	0	0	0	0	0	0	0	0
SAGE-547 U.S. Sales (SRSE)	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0
Total SAGE-547 U.S. Sales	$0	$0	$57,795	$151,799	$350,856	$670,199	$1,144,180	$1,202,075	$1,262,900	$1,326,803	$1,393,939
SAGE-547 ex-U.S. NPV Valuation											
Patients with Status Epilepticus	97,268	99,213	101,197	103,221	105,285	107,391	109,539	111,730	113,964	116,244	118,569
% of pts successfully treated with Benzodiazepenes	67%	67%	67%	67%	67%	67%	67%	67%	67%	67%	67%
Patients that may develop 2nd-line Status Epilepticus (SE)	32,487	33,137	33,800	34,476	35,165	35,869	36,586	37,318	38,064	38,825	39,602
% of patients successfully treated with 2nd line AEDs	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%
Patients that develop Refractory Status Epilepticus (RSE)	22,741	23,196	23,660	24,133	24,616	25,108	25,610	26,122	26,645	27,178	27,721
% of patients successfully treated with burst suppression	28%	28%	28%	28%	28%	28%	28%	28%	28%	28%	28%
Patients that develop Super Refractory Status Epilepticus (SRSE)	16,374	16,701	17,035	17,376	17,723	18,078	18,439	18,808	19,184	19,568	19,959
Cost per year ($)	$55,000	$55,000	$55,000	$56,650	$58,350	$60,100	$61,903	$63,760	$65,673	$67,643	$69,672
Gross to net adjustment	80%	80%	80%	80%	80%	80%	80%	80%	80%	80%	80%
% penetration of patients with SRSE	0%	0%	0%	2%	10%	25%	35%	50%	50%	50%	50%
Patients on SAGE-547	0	0	0	348	1,772	6,454	9,404	9,592	9,784	9,980	
SAGE-547 ex-U.S. Sales	$0	$0	$0	$15,749	$82,732	$217,295	$319,606	$479,683	$503,955	$529,456	$556,246
% penetration of U.S. patients with RSE	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
RSE Patients on SAGE-547	0	0	0	0	0	0	0	0	0	0	0
SAGE-547 ex-U.S. Sales (SRSE)	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0
Total W.W. SAGE-547 Sales	$0	$0	$57,795	$167,548	$433,588	$887,494	$1,463,786	$1,681,759	$1,766,856	$1,856,259	$1,950,185
COGS (incl. royalties)	$ 0.0	$ 0.0	$ 8,669.3	$ 25,132.3	$ 65,038.2	$ 133,124.0	$ 219,567.9	$ 252,263.8	$ 265,028.3	$ 278,438.8	$ 292,527.8
COGS	5%	5%	15%	15%	15%	15%	15%	15%	15%	15%	15%
Sales Force	0	40	100	100	100	100	100	100	100	100	100
Cost per rep	200	200	200	200	200	200	200	200	200	200	200
SG&A Additional Cost	2,000	2,000	10,000	15,000	15,000	15,000	15,000	15,000	15,000	15,000	15,000
R&D	43,000	37,000	41,255	45,381	47,650	60,000	50,000	40,000	40,000	40,000	40,000
Operating	$ -	$ (45,000)	$ (47,000)	$ (22,129)	$ 62,036	$ 285,900	$ 659,370	$ 1,159,218	$ 1,354,495	$ 1,426,827	$ 1,502,820	$ 1,582,657
Taxes	36%	0%	0%	0%	0%	36%	36%	36%	36%	36%	36%	36%
NPV/Year		$ (44,999.72)	$ (47,000)	$ (22,129)	$ 62,035.61	$ 182,976	$ 421,997	$ 741,900	$ 866,877	$ 913,169	$ 961,805	$ 1,012,901

Model Assumptions

Approval	Late 2017 in U.S.; Late 2018 E.U.
% SE patient growth	2%
Price	$55,000
Avg annual price increase	3%
Penetration	Quick ramp to 50%
Sales Force	Assume relatively small salesforce (100 persons)
Peak penetration	65% U.S.; 50% E.U.

Appendix
Overview of FDA Expedited Programs

	Fast Track	Breakthrough Therapy	Accelerated Approval	Priority Review
Nature of Program	Designation	Designation	Approval Pathway	Designation
Qualifying Criteria	A drug that is intended to treat a serious condition ***and*** nonclinical or clinical data demonstrates the potential to address unmet medical need ***or*** A drug that has been designated as a qualified infectious disease product	A drug that is intended to treat a serious condition ***and*** preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies	A drug that treats a serious condition, generally provides a meaningful advantage over available therapies, ***and*** demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality that is reasonably likely to predict an effect on IMM or other clinical benefit (i.e., an intermediate clinical endpoint)	An application for a drug that treats a serious condition ***and,*** if approved, would provide a significant improvement in safety or effectiveness
Time to Submit a Request	With IND or after Ideally, no later than pre-BLA or pre-NDA meeting	With IND or after Ideally, no later than the end-of-Phase II meeting	The sponsor should ordinarily discuss the possibility of accelerated approval with the review division during development	With original BLA, NDA, or efficacy supplement
Timelines for FDA Response	Within 60 calendar days of receipt of the request	Within 60 calendar days of receipt of the request	Not specified	Within 60 calendar days of receipt of original BLA, NDA, or efficacy supplement
Features	Actions to expedite development and review Rolling review	Intensive guidance on efficient drug development Organizational commitment Rolling review Other actions to expedite review	Approval based on an effect on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict a drug's clinical benefit	Designation will be assigned at the time of original BLA, NDA, or efficacy supplement filing

Source: FDA Web site

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DJIA:	1,7959.03
S&P 500:	2,089.27
NASDAQ:	4,992.38

The prices of the common stock of other public companies mentioned in this report follow:

GlaxoSmithKline	$48.21
Marinus Pharmaceuticals, Inc.	$9.31
Novartis AG	$99.87
Zogenix, Inc. (Outperform)	$1.36

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Coverage Universe	Percent	Inv. Banking Relationships*	Percent
Outperform (Buy)	65%	Outperform (Buy)	16%
Market Perform (Hold)	32%	Market Perform (Hold)	2%
Underperform (Sell)	2%	Underperform (Sell)	0%

*Percentage of companies in each rating category that are investment banking clients, defined as companies for which William Blair has received compensation for investment banking services within the past 12 months.

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in earnings estimates, valuation (and our valuation methodology), and other factors. Outperform (O) – stock expected to outperform the broader market over the next 12 months; Market Perform (M) – stock expected to perform approximately in line with the broader market over the next 12 months; Underperform (U) – stock expected to underperform the broader market over the next 12 months; not rated (NR) – the stock is not currently rated. The valuation methodologies used to determine price targets (where used) include (but are not limited to) price-to-earnings multiple (P/E), relative P/E (compared with the relevant market), P/E-to-growth-rate (PEG) ratio, market capitalization/revenue multiple, enterprise value/EBITDA ratio, discounted cash flow, and others.

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