COWEN
AND COMPANY

Biotechnology

Sage Therapeutics

Equity Research

Initiating Coverage

May 28, 2015

Price: $69.64 (05/27/2015)

Price Target: $95.00

OUTPERFORM (1)

Ritu Baral
646.562.1379
ritu.baral@cowen.com

Elyse Shapiro
646.562.1426
elyse.shapiro@cowen.com

Key Data

Symbol	NASDAQ: SAGE
52-Week Range:	$73.91 - 24.25
Market Cap (MM):	$1,975.5
Net Debt (MM):	$(127.8)
Cash/Share:	$4.99
Dil. Shares Out (MM):	28.4
Enterprise Value (MM):	$1,862.3
ROIC:	NA
ROE (LTM):	NA
BV/Share:	$4.15
Dividend:	NA

FY (Dec)	2014E	2015E	2016E
Earnings Per Share			
Q1	-	(0.66)A	-
Q2	-	(0.73)	-
Q3	-	(0.79)	-
Q4	-	(0.84)	-
Year	(1.67)A	(3.02)	(3.34)
P/E	NM	NM	NM
Consensus EPS	-	(2.79)	(3.35)

Consensus source: Thomson Reuters

Revenue (MM)			
Year	0.0	0.0	0.0

Initiate with Outperform, $95 Target: Potential Paradigm Change for SRSE

The Cowen Insight

We are initiating on Sage with an Outperform and $95 target. We think Ph3 SAGE-547 could be a paradigm-changing new treatment for super-refractory status epilepticus (SRSE), significantly decreasing associated mortality and morbidity. Based on strong Ph1/2 data, we think '547 could see wide use in SRSE with ~$1B peak sales.

Sage's GABA Platform Lead Candidate '547 Could Be Game Changer in SRSE

SAGE-547 (proprietary formulated allopregnanolone) is a neurosteroid entering Ph3 development in 2H15 for super-refractory status epilepticus (SRSE). SRSE is a condition of constant seizure (often related to acute neurological conditions) that has been unresponsive to 3 lines of previous treatment. We think '547 could become part of standard of care for SRSE, given clear unmet need for new treatments. SRSE has 40%+ mortality rates and high disability burdens. Current SRSE standard of care consists of medically induced coma.

SAGE-547 Ph1/2 Efficacy and Safety Data To Date Has Been Very Strong, Bodes Well for Imminent Ph3 Trial Which Could Produce Data in 2H16

The Ph1/2 trial of '547 in SRSE showed a 77% wean success rate, much higher than the ~20% response rate suggested by KOL natural history experience. All of patients successfully weaned remained relapse-free after 7 days. '547 was also associated with neurological functional improvements in responders. We are optimistic for the upcoming Ph3 trial based on previous Ph1/2 data and the Ph3 trial design (same inclusion/exclusion criteria as the Ph1/2 with very conservative powering assumptions). We model a 65% chance of success for '547 in the US.

'547 Could See ~$1B Peak WW Sales; Orphan Pricing Supported By Strong Pharmacoeconomic Arguments

We think '547 would be widely used in SRSE, and likely used early in a patient's disease course. SRSE is treated in the ICU, which is associated with significant cost (~$7-10K per day). SRSE patients' length of stay in the ICU is currently on average 21 days, which '547 has the potential to significantly shorten. We think '547 could be priced at ~$60K per treatment course in the US and even at that price, could generate significant pharmacoeconomic benefit. We see potentially high use rates as '547's may improve quality of care while reducing costs.We also think '547 may be effective in earlier-line refractory status epilepticus (RSE) and could see clinician directed use there. We model peak market share of '547 in SRSE at 75% and peak US and EU sales of $856MM and $221MM, respectively.

'547 Follow On Indications; GABA Pipeline Compounds Represent Upside

RSE and orphan epilepsies are large markets with unmet need. '547 provides a proof of concept for SAGE's GABA-based platform. SAGE-689 is in IND-enabling studies as an adjunctive treatment to RSE, and SAGE-217 is in IND enabling studies for orphan epilepsies such as Dravets and Rett syndromes. Sage is also evaluating '547 in essential tremor and postpartum depression.

At A Glance

Our Investment Thesis

We think Ph3 SAGE-547 could be a paradigm-changing new treatment option for super-refractory status epilepticus (SRSE), significantly decreasing the mortality and morbidity associated with the condition. Based on the strength of the Ph1/2 produced to date, we are optimistic for Ph3 success and think the drug could see widespread use in SRSE with ~$1B peak sales. We think '547 success derisks the remainder of SAGE's GABA-based platform, at least for the indications related to seizure. '689 and '217 are in IND enabling studies as adjunctive treatments to RSE and orphan epilepsies, respectively.

Forthcoming Catalysts

- SAGE-547 Ph3 Data (2H16)
- SAGE-689 IND (2H15)
- SAGE-217 IND (2H15)
- Sage announces additional follow-on compounds (2016)

Base Case Assumptions

- SAGE-547 is safe, effective, and superior to standard of care with efficacy similar to Ph1/2 data (~75% response rate)
- SAGE-689 and sage-217 are safe and well tolerated and generate solid clinical efficacy data

Upside Scenario

- SAGE-547 achieves higher than expected pricing and extremely high penetration rate, including potential earlier line use.
- SAGE-547 is effective in other indications
- Sage's follow-on compounds quickly generate impressive clinical data in multiple other indications

Downside Scenario

- SAGE-547 fails the current Ph3 clinical trial
- SAGE-547 is not approved by the FDA and/or EMA
- SAGE-547 does not achieve expected pricing
- SAGE-547 does not achieve high levels of uptake

Price Performance

Source: Bloomberg

Company Description

Sage Therapeutics focuses on developing novel therapeutics for CNS-related indications with clear a unmet need. Lead compound SAGE-547 is in Ph3 for Super Refractory Status Epilepticus (SRSE), a disease that affects ~25K individuals/year in the US, and has high mortality and very poor current treatment options. Follow-on GABA-ergic compounds SAGE-689 and SAGE-217 are in development for Refractory Status Epilepticus (RSE) and orphan epilepsies, respectively. Sage also plans to develop an NMDA-receptor related compound.

Analyst Top Picks

	Ticker	Price (05/27/2015)	Price Target	Rating
Amicus Therapeutics	FOLD	$11.96	$19.00	Outperform
Cempra	CEMP	$36.56	$43.00	Outperform

Investment Thesis

We think Sage Therapeutics' SAGE-547 (allopregnanolone) will become a backbone of treatment for super-refractory status epilepticus

SAGE-547 is a proprietary formulation of a naturally occurring neurosteroid (allopregnanolone in Captisol) with patent protection out to at least 2033. The drug is a first-in-class potential therapy for super refractory status epilepticus, a severe state of continuous seizure unresponsive to first-, second-, and third-line therapies. '547 is currently starting a placebo-controlled Phase 3 study that we think will be successful and be the only pivotal trial required to support FDA and EMA approval in the late 2017 or 1H18 timeframe. We expect neuro-intensivists to add '547 to the current 4th-line treatment paradigm to greatly improve patient recovery from current dismally low rates.

Super-refractory status epilepticus represents a poorly-understood, major unmet need

Much remains unknown about the pathology and mechanism of status epilepticus (SE), much less super-refractory status epilepticus (SRSE). However, much is understood about the mechanisms that have been proven to control SE and SRSE. As a result, we think SAGE-547 has excellent scientific rationale for SRSE. The compound is thought to act through activation of extra-synaptic GABA-A receptors. While the compound also works on intra-synaptic GABA-A receptors (the receptors through which first-line agents, benzodiazepines, work), these receptors are internalized largely within 30 minutes of status epilepticus onset, necessitating treatment with 2nd line treatments (phenytoin and fosphenytoin). ~20% of SE patients do not respond to either 1st or 2nd line therapy, and are then diagnosed as refractory status epilepticus (RSE). Current 3rd-line and beyond treatment consists of medically-induced coma and temporally-spaced 'wean' attempts, where anesthesia is reduced and patients hopefully emerge from coma without epileptic brain activity re-emerging. ~40% of total RSE patients (or 5-10% of total SE patients) are unable to be successfully weaned on the 1st attempt and are then classified as SRSE. SRSE has a 40+% mortality rate, which is highly dependent on the etiology of the SE.

We think SAGE-547's Ph1/2 trial gives excellent positive precedent data for Ph3 development

547's Phase 1/2 trial in SRSE patients showed a 77% wean success rate (17/22 evaluable trial patients), well above the rate suggested by SRSE natural history. Epilepsy and SE KOLs that we spoke to believe the recovery rate of the ~22 patients in the Ph1/2 study would likely have been only ~20% or even less. One of the most important contributors to potential successful outcomes (successful wean from coma) for these patients is the underlying etiology of the SE (e.g. infectious, autoimmune, or cerebrovascular origins). We think the distribution of underlying etiologies is relatively representative of the overall SRSE population save for the exclusion of anoxic patients (who have a particularly poor prognosis). Functional improvements in the responder group (as measured by GCI-S and Glasgow Coma Scale) were also impressive with 41% of responders (7/17) achieving a full response (15/15) on the GCI-S compared to only 1 of 5 non-responders.

Further, all of the patients who were successfully weaned remained relapse free after 7 days. 4 patients relapsed, which represents ~24% of the successfully weaned population and 18% of the evaluable population. We think this relapse rate compares favorably with the historically observed rate in SRSE (20%+ as suggested by our KOLs) and even the less severe SE population (13% per the widely cited Richmond SE epidemiology study).

The safety profile of the '547 has also proven to be particularly benign, with no commonly occurring side effects noted to occur with use in what we note to be a particularly fragile and sick patient population. While one case of fever and another case of elevated BUN was attributable to drug by the investigator, other KOLs we spoke to familiar with the trial doubt the AE is related to drug. We view the new SAGE-547 Ph3 trial as well designed with a high chance of success.

We think SAGE's newly announced placebo-controlled Ph3 study is well designed and has a high chance of clinical success. The entry criteria of the Ph3 study is very similar to the entry criteria of the successful open-label Ph1/2 trial just completed. Importantly, it has the same inclusion/exclusion criteria (particularly the same anoxia exclusion criteria) as the previous study. We also believe Phase 3 study powering was skewed conservative as they are assuming a 35% placebo response rate. Per the phase 3 study protocol, all weans during study will be at least 2nd attempt weans, which KOLs indicate have only about a 20-25% success rate, lower than the trial's assumption. The trial is 90% powered and assumes a 35% placebo response rate.

We think SAGE-547 would see very wide use in SRSE; our consultants think there is already strong interest in its potential application in RSE

There is significant enthusiasm amongst KOLs for the use of SAGE-547 in SRSE since they see such a massive unmet need in the condition. There is significant frustration with the current treatment option of medical coma, which is viewed as a stop-gap measure. They view response and recovery rates for SRSE as very poor, and mortality is generally regarded as ~50% or greater, with 70% or more of patients experience serious prolonged neurological and functional deficits. Older patients, especially those with acute cerebrovascular events that precipitated the current SE event have particularly poor outcomes with current treatment paradigms. Given the potential for cost-savings with the drug (ICU and neurocritical care can cost $7-10K per day), we think the drug would be used almost immediately after first wean failure.

One almost universal belief amongst KOLs is that the more time a patient spends in seizure, the worse their mortality or outcomes. As such, many KOLs are already speculating about the use '547 in RSE even before the first coma wean attempt. We suspect that if ICU cost and reimbursement is not an issue, there could be clinician directed alternate use in earlier stages of SE, before patients achieve super-refractory status.

Overall, we think SAGE-547 could reach peak market share of 75% in SRSE, translating to $856M in peak US sales

Our KOL consultants have indicated to us that ICUs and neuro-critical care units are some of the most price-insensitive divisions of a hospital. Given the previously described cost of ICU and neurocritical care, and potential shortening of stay and improved outcomes suggested by the Ph1/2 data to date, we think '547 could be priced at ~$60K per treatment course in the US and still generate significant pharmacoeconomic benefit from use. We see high penetration in SRSE patients since it would simultaneously improve quality of care and reduce care costs. As such we see peak US market share at 75% and EU market share at 60%. This could result in US peak sales of $856MM and EU peak sales of $221MM.

We also think SAGE's preclinical pipeline neurosteroid products have significant potential in treating earlier stage status epilepticus

'547 in SRSE provides proof of concept for GABA-based platform. The majority of SAGE's platform is based upon modulating the GABA receptor in order to resolve seizures and other CNS disorders. We think 547, if effective, could de-risk the rest of SAGE's pipeline, at least for the indications related to seizure. Because there are similarities between SAGE's '547, '689 (IND enabling as an adjunctive treatment to SE), and '217 (IND enabling for orphan epilepsies), our confidence in follow-on compounds would increase if '547 produces positive, meaningful, results.

SAGE's initial strategy is based on pursuing less common diseases with clear unmet needs. Given Sage's streamlined portfolio, we think it is an attractive take-out target, especially if '547 proves successful. Any company looking to expand or build an epilepsy franchise could incorporate all of SAGE's compounds into their portfolio without the need to abandon any of their previous development efforts.

2015/2016 are catalyst-heavy for SAGE, which could garner investor confidence and attention. SAGE plans to initiate enrollment in its Ph3 SAGE-547 in mid-2015, and we expect data in 2016. Sage also plans to file an IND for SAGE-217 in late 2015 for patients with rare orphan epilepsies.

Company Description

SAGE Therapeutics is developing novel medicines to treat life-threatening, rare, CNS disorders. Their proprietary platform generates compounds that target GABA-A and NMDA glutamate receptors, which play key roles in many psychiatric and neurological diseases. Lead compound '547 is in Phase 3 for super-refractory status epilepticus (SRSE), a severe epileptiform disorder that has high mortality and poor treatment options. '547 will also be investigated for essential tremor and post-partum depression, with Phase 2s in those indications starting shortly. Follow-on compound '217 is a neuroactive steroid that is in IND-enabling studies to support clinical development of orphan epilepsy disorders such as Rett and Dravet Syndromes. SAGE-689 is in IND-enabling studies as an adjunctive IV for the treatment of status epilepticus.

Financials

We reach our $95 price target for SAGE on a pNPV basis. All of the value in our pNPV is attributed to SAGE-547 ($79 from US sales, $16 from EU sales). We assume a 65% and 60% probability of success in the US and EU, respectively. We estimate peak US sales of $856MM at a 75% market share, and EU sales at $221MM, at a 60% market share.

We model an increase in R&D spend through 2016, attributable to the ongoing Ph3 in '547 as well as studies in follow-on compounds '217 and '689. We assume an increase in SG&A in 2017 and a more significant ramp-up 2018 to prepare for the launch of '547.

We model peak sales of SAGE-547 at $856MM in the US and $221MM in the EU. We model 75% and 60% market share in the US and the EU. SAGE can charge orphan pricing and build a streamlined salesforce to bring SAGE-547 to physicians and patients. About 900 US hospitals are responsible for 70% of SRSE discharges, enabling SAGE to train and use a relatively small salesforce.

As of March 31, 2015, Sage had cash of $113.2MM. A recently completed cash offering will add approximately $129.2MM in net proceeds to Sage's cash position. Sage's current cash position should be sufficient to fund operations through mid-2017. 1Q15 cash burn was $14.6MM, which we expect to increase substantially as the '547 Phase 3 trial is initiated.

SAGE Quarterly P&L

	2013A	2014A	1Q15A	2Q15E	3Q15E	4Q15E	2015E
Revenues							
SAGE-547 for SRSE	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total Revenues	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
Operating Expenses							
R&D	14.4	24.1	12.9	15.0	17.0	19.0	63.9
G&A	3.9	9.7	4.0	4.0	4.0	4.0	16.0
Total Operating Expenses	**18.3**	**33.8**	**16.9**	**19.0**	**21.0**	**23.0**	**79.9**
Loss from Operations	(18.3)	(33.8)	(16.9)	(19.0)	(21.0)	(23.0)	(79.9)
Interest income (expense)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
other income (expense)	(0.0)	(0.0)	0.0	0.0	0.0	0.0	0.0
Net loss	**(18.3)**	**(33.8)**	**(16.9)**	**(19.0)**	**(21.0)**	**(23.0)**	**(79.9)**
Accretion of convertible preferred stock to redemption value	(0.0)	(2.3)	0.0	0.0	0.0	0.0	0.0
Net loss attributable to common stockholders	(18.3)	(36.1)	(16.9)	(19.0)	(21.0)	(23.0)	(79.9)
EPS (basic and diluted)	**$ (12.26)**	**$ (1.67)**	**$ (0.66)**	**$ (0.73)**	**$ (0.79)**	**$ (0.84)**	**$ (3.02)**
Number of shares (basic)	1.49	21.57	25.66	26.17	26.69	27.23	26.43
Number of shares (diluted)	1.49	21.57	25.66	26.17	26.69	27.23	26.43

Source: Cowen and Company

SAGE Annual P&L

	2013A	2014A	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E
Revenues										
SAGE-547 for SRSE	0.0	0.0	0.0	0.0	0.0	98.3	440.2	767.6	1,020.7	1,047.2
Total Revenues	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**98.3**	**440.2**	**767.6**	**1,020.7**	**1,047.2**
Operating Expenses										
R&D	14.4	24.1	63.9	80.0	70.0	55.0	158.5	138.2	102.1	78.5
G&A	3.9	9.7	16.0	18.0	25.0	40.0	40.0	40.0	40.0	40.0
Total Operating Expenses	**18.3**	**33.8**	**79.9**	**90.0**	**95.0**	**95.0**	**198.5**	**178.2**	**142.1**	**118.5**
Loss from Operations	(18.3)	(33.8)	(79.9)	(90.0)	(95.0)	3.3	241.7	589.5	878.6	928.6
Interest income (expense)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
other income (expense)	(0.0)	(0.0)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Net loss	**(18.3)**	**(33.8)**	**(79.9)**	**(90.0)**	**(95.0)**	**3.3**	**241.7**	**589.5**	**878.6**	**928.6**
Accretion of convertible preferred stock to redemption value	(0.0)	(2.3)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Net loss attributable to common stockholders	(18.3)	(36.1)	(79.9)	(90.0)	(95.0)	3.3	241.7	589.5	878.6	928.6
EPS (basic and diluted)	**$ (12.26)**	**$ (1.67)**	**$ (3.02)**	**$ (3.34)**	**$ (3.45)**	**$ 0.12**	**$ 8.45**	**$ 20.20**	**$ 29.51**	**$ 30.58**
Number of shares (basic)	1.49	21.57	26.43	26.96	27.50	28.05	28.61	29.19	29.77	30.37
Number of shares (diluted)	1.49	21.57	26.43	26.96	27.50	28.05	28.61	29.19	29.77	30.37

Source: Cowen and Company

SAGE pNPV

Assumptions / Results	
NPV (US$)	**94.88**
Current price (US$)	67.00
Upside (Downside)	**42%**
NoSH	25.7
Current market cap (US$m)	
Implied market cap (US$m)	
Pharma PE	15.0x
Discount rate	20.0%
Current year	2015.25

Drug name	Indication	Status	Estimated launch	Years to Launch	Years to Peak Sales	Success?	Peak Sales (US$m)	Probability weighted Peak Sales (US$m)	Royalty	Profitability	Probability weighted Peak Profit (US$m)	Discount Factor	NPV (US$)
SAGE-547	SRSE (US)	Phase 3	2018	2.8	7.8	65%	856	556	100%	100%	556.23	4.11	79.16
	SRSE (EU)	Phase 3	2019	3.8	8.8	60%	221	133	100%	100%	132.52	4.93	15.72
												Total	94.88

Source: Cowen and Company

Super-Refractory Status Epilepticus (SRSE) and SAGE-547

Super-Refractory Status Epilepticus: Super-Refractory Status Epilepticus (SRSE) is a severe stage of sustained status epilepticus (SE) that has not responded to multiple escalating lines of treatment. SE (defined for this report as general convulsive or general non-convulsive) is relatively easily to diagnose with observation, as it is defined as state of continuous seizure lasting 5 minutes or more, or relapsing seizure without regaining consciousness between episodes. Patients have initial seizures that cause them to lose consciousness, exhibit tonic-clinic muscle activity, tongue biting and urinary incontinence. As the seizure progresses for a longer period of time, general convulsive activity is less obvious, such as twitching of eyelids only. Non-convulsive status epilepticus does occur and can be harder to diagnose, with symptoms include blunting of consciousness, agitation, abnormal eye movement, aphasia, and abnormal limb posturing. Diagnosis of non-convulsive SE requires EEG examination.

AED Therapy Varies In Its Effectiveness Depending On Seizure Type

Seizure Type	Subtype	% Total Epilepsy Patient Population	% Controlled on AED Therapy
Partial	Simple Partial		
	Complex Partial	20%	
Generalized	Absence	25%	40-75%
	Tonic-Clonic	60-90%	50-85%
Mixed		30%+	
Refractory		30%	
Total		**100%***	**60-70%**

* Numbers do not add to 100% because many sufferers have more than one seizure type.

Source: BMJ, Merck Manual, Postgraduate Medicine's Seizure Management Symposium, U.S. Pharmacist.

Etiology: While patients with a history of epilepsy can develop SE, about ~40% cases occur in patients without previous history of epilepsy. Most cases of SE are associated with an acute event or insult, especially cases in patients without a history of epilepsy. Causes include CNS infection, large ischemic stroke, intracranial hemorrhage, severe systemic infection, malignant brain tumor, AIDS with CNS complications, and intracranial tumors. SE can also be caused by inadequate plasma levels of anti-epileptic drugs in epileptic patients (usually a result of non-compliance) or alcohol/drug abuse.

Incidence: In the US, about 41 per 100,000 experience SE (higher than the EU because of a more mixed Caucasian and African American population), and EU, between 15 and 20 per 100,000 will experience SE (as reported in studies from Central Europe). This translates to about 100,000-150,000 cases of SE. Over 60% are well treated by first-line treatment, and do not progress to more refractory disease.

Prognosis and Outcomes: SE is associated with in-hospital mortality rates between 9.4% and 21%, and the 30-day mortality rate falls in a range of 19% to 27%. SE accounts for about 20% of ER visits for neurological issues.

Etiology of a patient's SE plays an important role in the patient's outcome. Patients with anoxia and other medical conditions such as encephalitis tend to fare poorly. Those with strokes, tumors, and traumas usually have an intermediate mortality. The etiology that tends to fare best is in patients with underlying epilepsy with some exacerbating factor causing the SE or those related to alcohol or drug abuse. SE linked to infection tends to have a lower mortality in SE but has a higher mortality rate in adults.

Treatment: Usually, IV benzodiazepines are given as a first line agent, and antiepileptics are delivered as a second line agent (IV phenytoin, fosphenytoin, phenobarbital, or valproic acid). The importance of prompt treatment with benzodiazepines has become better understood over time. Benzodiazepines work primarily through intra-synaptic GABA-A receptors, which inhibit synaptic (and therefore seizure) activity. However, these receptors start being internalized into the neuron starting from about 5 minutes into an SE episodes, resulting in increasing resistance to benzodiazepines over the course of an SE episode. It is therefore a critical part of the SE treatment paradigm to start treatment as soon as possible.

Etiology and Mortality of SE

Etiology and Mortality of SE		
Mortality Risk	Underlying Etiologies	% of cases
High	Anoxia	5
	encephalitis	25-50
Medium	Stroke	19-30
	Tumor	10
	CNS or systemic infection	10
	Trauma	3
Low	Previous epilepsy	0
	Low levels of AEDs	0
	Drug overdose	3
	Alcohol Withdrawl	0-8

Source: Cowen and Company

Refractory status epilepticus: Refractory status epilepticus (RSE) is defined variably in the literature. Most definitions refer to either a seizure that does not respond to 2 or 3 different antiepileptic medications. Some older definitions define RSE as ongoing seizure activity for 1-2 hours (ostensibly while various medications are administered but fail to control the seizure).

Prevalence: Of patients with SE, about 30-40% develop RSE, which translates to about ~50,000 cases in the US annually.

Treatment: If a second line agent (described above) fails, a patient will receive anesthesia and can be put into a medically induced coma. The most common anesthetics used for coma induction are propofol and barbiturates. In some uses midazolam (a benzodiazepine) is used in combination with one of the previous agents. Each of the previous agents is associated with drawback. Propofol is generally favored amongst our SRSE KOL consultants, although it can be related to Propofol-related infusion syndrome (PRIS), a mitochondrial toxicity related to the lipid content of IV propofol (necessary due to the highly hydrophobic nature of the compound). Phenobarbitol has very poor distribution characterization, quickly accumulating in adipose tissue, making tight control of plasma levels difficult. Midazolam meanwhile, is associated with very rapid levels of tolerance. Patients are generally treated until an EEG burst-suppression pattern is reached, which usually controls epileptiform activity. Very rarely are patients required to be sedated to the point of an iso-electric EEG pattern. The first wean attempt from the induced coma is usually made ~24 hours after burst suppression is achieved.

Prognosis/Outcomes: RSE is associated with poorer outcomes than SE, with mortality rates in the range of 23% to 61%. The mortality rate is independent of the treatment strategy given to the patient. Our KOL consultants believe underlying etiology has a substantially smaller impact on potential outcomes than in first-line SE.

Super-refractory Status Epilepticus: SRSE guidelines for diagnosis are mixed in the literature, and is defined as either failure of a third line treatment (recurrent SE after one or more wean attempts from medicinally induced coma), or seizures continuing beyond 24 hours after initiation of an anesthetic agent.

The mortality rate of SRSE patients is about 42%.

Status Epilepticus Progression

Stage	Time	Physiological Response
1	msecs-secs	Protein phosphorylation Ion channel opening and closing NT release
2	secs-mins	Receptor trafficking Decrease in inhibitory GABAA Increase in excitatory NMDA receptors Increase in excitatory AMPA receptors
3	mins-hrs	Neuropeptide expression Increase in excitatory substance P Insufficient replacement of inhibitory neuropeptide Y
4	days-wks	Genetic and epigeneetic changes Changes in gene expression DNA methylation Regulation of microRNA

Source: Cowen and Company, adapted from Betjemann, et al., 2015

Status Epilepticus Treatment Paradigms, by Stage

Time	Disease Stage	Treatment Examples	Treatment Type	Notes
5-30 mins	Early SE	Lorazepam, midazolam, diazepam	Benzodiazepines	
30-120 mins	Established SE	Benzos + phenytoin, fosphenytoin, phenobarbital, valproate	IV-antiepileptics	
>120 mins	Refractory SE	Benzos + IV antiepileptics + propofol, midazolam, phenobarbital	General anasthesia	Wean attempts every 24 hrs
24 hrs	Super-Refractory SE	Continue Tx, Seizure has continued/recurred		Wean attempts every 5 days

Source: Cowen and Company

Pathology of SRSE

GABA is the principal inhibitory neurotransmitter (NT) in the cerebral cortex. It acts to counterbalance neuronal excitation. If there is an imbalance, specifically a deficiency in GABAergic activity, too much neuronal excitation can cause seizure. GABA is formed within the GABAergic axon terminals and release into the synapse. It acts on either GABA-A or GABA-B receptors. GABA-A, which controls chloride entry into the cell, influences the early portion of GABA-mediated inhibitory pre synaptic potential.

GABA-B, which increases potassium conductance, decreases calcium entry, and inhibits the presynaptic release of other neurotransmitters, influences the later portion.

GABA is abundant in the brain and hyperpolarizes inhibition of almost all neurons. It is removed by uptake into glia and presynaptic nerve terminals and is catabolized by GABA transaminase. Prolonged epileptiform bursting results in internalization of intrasynaptic GABA-A receptors and a resulting reduction of GABA-mediated synaptic inhibition. Constitutive internalization of GABA-A is quick and occurs more rapidly with the increased neuronal activity attributable to seizures. Thus, the inhibition of neuronal activity (by benzodiazepam seizure control) reduces the rate of internalization, and GABA-A internalization is likely regulated by neuronal activity.

GABA receptor mediated inhibition is partially responsible for ending seizures normally. NMDA receptor activation by glutamate may be required for seizure continuation. The activation of NMDA increases intracellular levels of calcium, which could contribute to the nerve cell injury that afflicts patients with SE. When seizures are later stage, longer, and more difficult to control, there is likely a mechanistic shift from not enough GABAergic mediated transmission inhibition to excessive NMDA excitatory receptor mediated transmission. This could explain, at least in part, why GABAergic mechanisms are less effective in later-stage SE patients.

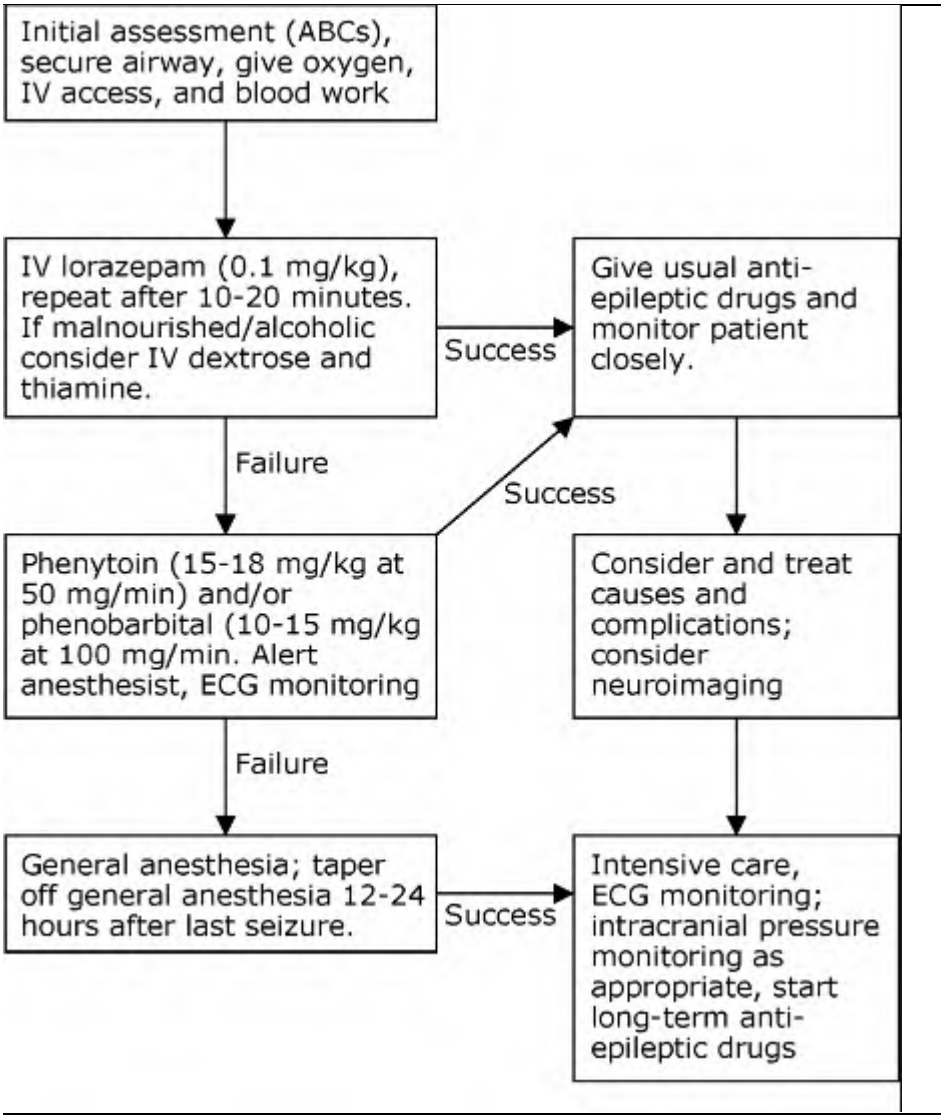
SE results in significant cerebral damage. Neuronal cell necrosis, gliosis, and network reorganization are the hallmarks of damage caused by SE. It has been suggested that the high levels of excitotoxicity initiate the process of cell death. This is driven by excessive glutaminergic receptor over-activity and causes a harmful influx of calcium into the cells that causes necrosis or apoptosis. Necrosis and apoptosis can trigger cascade of mitochondrial dysfunction, release of neurotrophins and neurohormones, inflammatory reactions, dendritic remodeling, neuromodulation, immunosuppression, and the activation of a few molecular signaling pathways that lead to programmed cell death. For this reason, EEG burst suppression is generally recommended before halting treatment.

Treatment

The initial goal of treatment of SE, RSE and SRSE, as previously stated, is to stop clinical and electrographic seizure activity before determining and ameliorating the cause of the SE. Seizures lasting longer than 5 minutes are harder to control and are associated with worse outcomes. After about 30 minutes, cerebral metabolic decompression occurs, and the window for effective treatment is highly limited.

Most treatment begins with benzodiazepines, and then IV antiepileptic drugs (phenytoin, phenobarbital, valproate). If necessary, anesthesia is delivered to patients. After terminating SE, treatment goals include: preventing seizure recurrence, management of precipitating causes, management of complications.

General SE Treatment Algorithm



Source: http://nihlibrary.ors.nih.gov/jw/POC/eepSE.htm

Benzodiazopines elicit a GABAergic inhibition and are less effective in more advanced SE because they have no influence over the NMDA glutamate receptor. They are GABA-A agonists and therefore inhibit neuronal firing. In later stage diseases, NMDA antagonists (such as ketamine) are potentially more beneficial.

Lorazepam is the preferred IV benzodiazepine and midazolam is the preferred IM therapy (but overall, lorazopam is the easiest to administer and controlled SE in about 65% of patients). Both lorazepam and midazolam have shown relatively equal efficacy. The rapid administration of benzodiazopines, however, can cause respiratory depression and hypotension. Both diazepam and midazolam have a rapid redistribution and a shorter duration of action.

Hydantoins are delivered if benzodiazopines do not stop seizure activity within 10 minutes or if a patient experiences intermittent seizures for about 20 minutes. Phenytoin or fosphenytoin are the most commonly used second-line therapies. Phenytoin is lipid soluble and reaches peak concentration in the brain about 15 minutes after IV administration, and fosphenytoin achieves therapeutic concentration in about 10 minutes. Less drug is found in active epileptogenic and damaged areas of the brain as it is dispersed to other regions. Phenytoin is difficult to control because of its metabolism and variability in patient-to-patient metabolism rate, and can also result in an idiosyncratic infusion reaction known as purple-glove syndrome. As a result, fosphenytoin is the preferred second-line SE agent today.

Most hydantoins are associated with the risk of hypotension, arrhythmia (QT prolongation). ECG, and arterial blood pressure monitoring are mandatory in patients who receive phenytoin. As mentioned, fosphenytoin is generally preferred from a safety and efficacy standpoint. Valproate sodium solution can also be used, but must be used cautiously in patients with traumatic head injury. Risks associated with valproate sodium are hyperammonemia, pancreatitis, thrombocytopenia, and hepatotoxicity. Topiramate can be delivered, but is less frequently used because no IV formulation is available, it cannot be used in pediatric patients, and can cause metabolic acidosis.

Anesthetic agents will eventually be able to control SE with a high enough dose, but can still fail to control SE because side effects which can limit dosing. They are only given if a second-line agent (antiepileptic) is ineffective. Barbiturate anesthetic agents include phenobarbital and thiopental. Phenobarbital is sometimes delivered by IV to control seizures if benzodiazepines and hydatonins fail. Phenobarbital acts by prolonging the inhibitory postsynaptic potential by acting on the intrasynaptic and potentially post-synaptic GABA-A chloride channels and reaches therapeutic levels within 3 minutes. Side effects include excess sedation, respiratory depression, hypotension, and drug-drug interactions. Further, because barbituates have zero-order kinetics, they have rapid redistribution, long half-lives and therefore long recovery periods. Anesthesia can persist for days, even after an infusion of only 12 hours.

Midalozam is another anesthesia, is delivered by IV, and rapidly enters the brain tissue with a shorter term duration of action. It binds to and enhances the GABA-A receptor. However, tolerance is a main disadvantage, which can lead to seizure relapse, and has a heightened risk of hepatic and renal impairment.

Propofol is a fast acting GABA-A modulator which allows for control of anesthesia level because of its shorter half-life. It can cause hypotension and/or cardiocirculatory depression, but less than that caused by barbiturates. Prolonged use of propofol can result in propofol infusion syndrome, which is a rare but potentially lethal side effect on mitochondrial and cellular metabolic function thought to be mediated by the lipid content of propofol formulations.

Ketamine is less studied but has shown efficacy in some SRSE cases. It acts on the GABA-A receptor and as an NMDA antagonist. Ketamine does not cause cardiac depression or hypertension. Further, the NMDA action is unique and can behave efficaciously in more progressed patients.

Anasthesia is usually continued until EEG burst suppression is reached. The dose is lowered in prolonged episodes after the initial burst suppression is achieved. Anasthesia is usually reversed initially every 24-48 hours, and if seizures recur, it is re-

established. Over time, the duration of individual cycles increased, and after a few weeks, anesthesia is often continued for 5 days before attempting to reverse it.

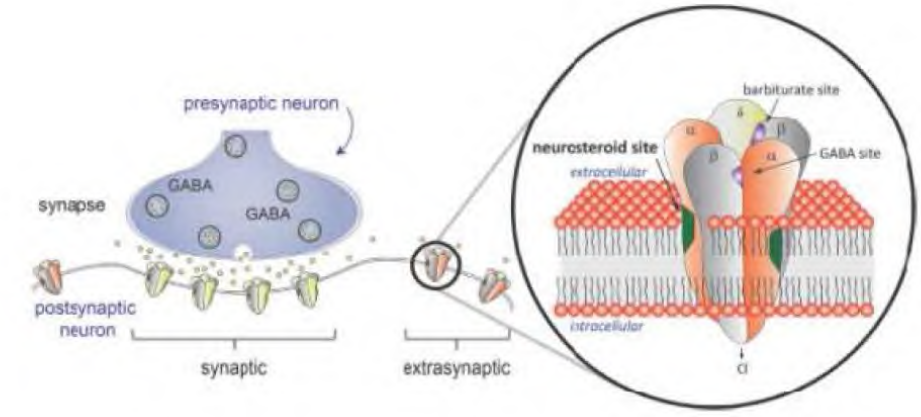
Eventually patients must be weaned off anesthesia (assuming this stage comes before organ failure). Rapid weaning is associated with high rates of recurrence or rebound seizures, and it is thus general practice to wean slowly over multiple days. In extremely prolonged cases of SE, the risks of continuing anesthesia are usually higher than the risk of ongoing SE. Nonetheless, withdrawal and restitution cycles of anesthesia are usually continued.

SAGE-547

SAGE-547 is a proprietary formulation of allopregnanolone, a naturally occurring neurosteroid and known metabolite of progesterone. It is an allosteric modulator of both synaptic and extra-synaptic GABA-A receptors. This is a unique feature not normally seen in orthosteric drugs, which function directly on either the synaptic OR extrasynaptic receptor. Orthosteric molecules' limited use and efficacy is linked to, in part, their complete activation or inhibition of a neuron with little ability for fine-tuning of neuronal signals or impact on the receptor at a site other than the native site.

When an orthosteric drug is delivered, neurons can be over-stimulated by a neurotransmitter (NT) or can be unable to respond to neurotransmission. Regulation of normal presynaptic and extrasynaptic rhythm of release of NTs and NT binding is crucial, especially in seizure and CNS disorders. '547's highly selective and modulatory control at the extrasynaptic GABA-A receptor is mechanistically superior to orthosteric drugs in its ability to exert more control over activity and in safety.

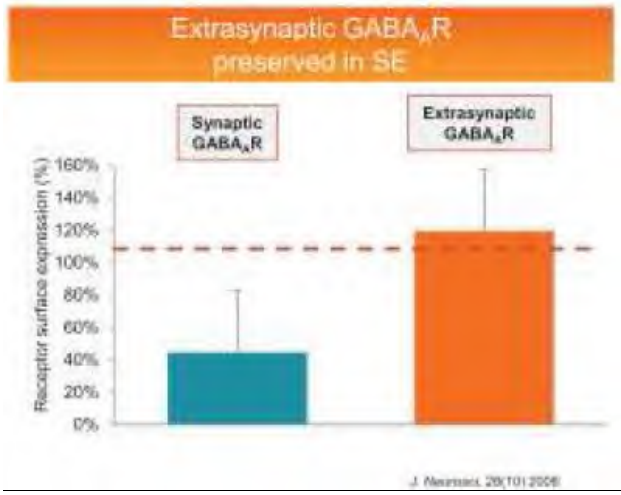
Presynaptic vs Extrasynaptic Activation



Source: SAGE

Unlike Benzodiazepines (BZDs), which act at the synaptic GABA-A receptor but not at extrasynaptic GABA-A receptors, '547 can mediate the activity of both. While BZDs are effective in earlier stage patients who benefit from the up-regulation of GABA-A receptors, patients approaching a refractory state have down-regulated or diminished GABA-A receptors. The extrasynaptic GABA-A receptor, however, remains intact during periods of prolonged seizure, so '547's unique ability to target these receptors could be differentially effective.

Extrasynaptic Activation Is Crucial



Source: SAGE

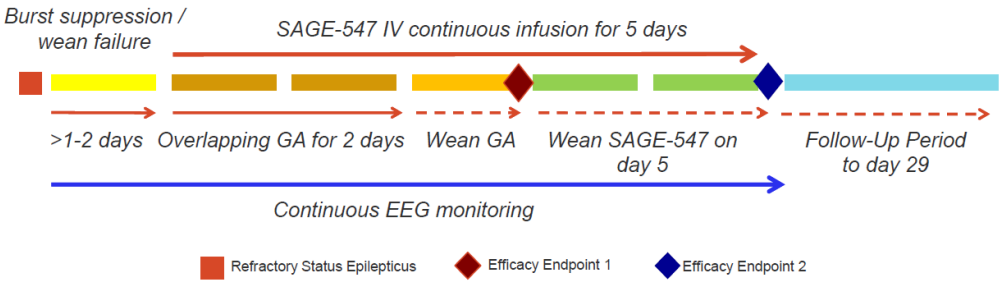
SAGE-547 has a wide therapeutic window to allow for GABA-A receptor modulation without inducing anesthesia, which gives it an advantage over available therapies that do induce anesthesia and are accompanied with anesthesia-related adverse events. The short half-life of one hour allows for continuous IV administration and allows a physician to tailor therapy to a patient's needs.

Clinical Data To Date

Ph1/2 Trial: Design and Data

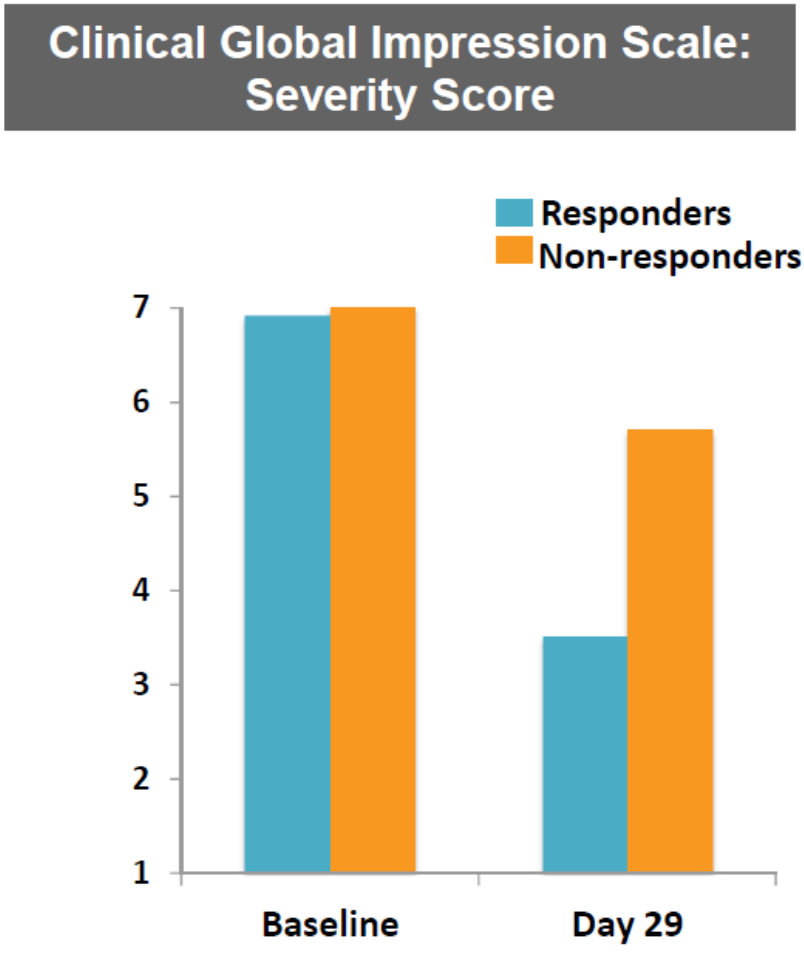
Design: The Ph1/2 open label trial investigated the safety, efficacy, and PK of 2 IV dose cohorts of SAGE-547 as an adjunctive therapy for patients with SRSE. The trial was performed at 18 trial sites, with a total enrollment of 25 patients (22 evaluable, 16 at standard 200 nM dose, 6 at higher 300 nM dose) who had failed first and second line agents and who failed IV general anesthesia administered over 24 hours. Patients were given SAGE-547 IV for 5 days while weaning off a third line IV general anesthesia. Patients were monitored for 30 days after treatment initiation. Patients whose SE was caused by anoxic brain injury or patients with end-organ damage were excluded from the trial. The primary endpoints were safety and tolerability (EEG, physical exams, neurological exams, vital signs, clinical lab measures, ECGs, and concomitant medication usage). Secondary endpoints were efficacy of SAGE-547 on SRSE by the need to place a patient back into a medically induced coma for seizure control, as well as a duration of observed response, global and specific cognition scales.

SAGE-547 Ph1/2 Trial Design



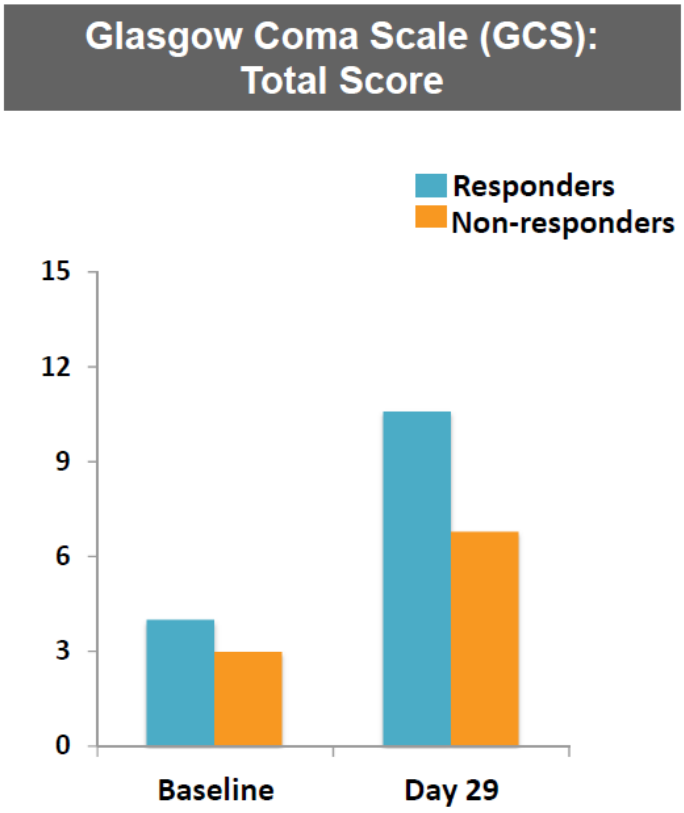
Source: Sage

CGI-S Improvement with SAGE-547



Source: Sage

Patient Improvement on Glasgow Coma Scale



Source: Sage

Efficacy: 77% (17/22) patients responded well to '547 and were successfully weaned off anesthetic agents. 81% of the low dose group responded; 67% of the high dose group responded (we note small numbers in the high dose group, which was only opened upon trial expansion). This response rate was well above the rate suggested by SRSE natural history. Epilepsy and SE KOLs that we spoke to believe the recovery rate of the ~22 patients in the Ph1/2 study would likely have been only ~20% or even less. One of the most important contributors to potential successful outcomes (successful wean from coma) for these patients is the underlying etiology of the SE (e.g. infectious, autoimmune, or cerebrovascular origins). We think the distribution of underlying etiologies is relatively representative of the overall SRSE population save for the exclusion of anoxic patients (who have a particularly poor prognosis).

There was no recurrence of SRSE in the 24 hours after treatment for any of the responders. There were 4 cases of recurrence in the day 7 to day 21 timeframe that occurred in the responder group, which we think is comparable to 'normal' responders. '547 was also associated with increased EEG suppression, with peak suppression occurring about 1 hour into the loading phase ($p<0.001$), and the effect was consistent in spite of different third-line agents used. Patients with the Glasgow scale rating of "most extremely" and "severely" ill had improved on average 3 points to the ""mildly ill " category, and continued to improve over the 29 days of follow up. Non-responders did not show significant clinical benefit.

Safety: SAGE-547 was relatively well-tolerated. 64% of patients had at least one SAE, none of which were determined to be related to the drug. 6 deaths were reported independent of treatment response but were caused by underlying conditions. The most common AEs were fever, hypotension, diarrhea, peripheral edema, anemia, and blood urea nitrogen (BUN) increases. Only one case of fever and one of BUN were found to be related to the drug by the reporting investigator, although other SRSE KOL consultants believe this is unlikely. Given the serious nature of SRSE, underlying conditions, and confounding safety variables such as other drugs delivered, we see '547 as having an extremely clean safety profile that we and physicians think are preferable to standard of care.

Emergency Use Experience

Sage compiled evidence of SAGE-547 in emergency-use settings for SRSE. 10 patients were treated under an emergency-use IND. Each individual case of SRSE resulted from a different underlying etiology. 7 of the 10 patients achieved resolution of SRSE during or soon after treatment, and one was not evaluable for efficacy.

Regulatory Path Forward—Ongoing Phase 3 Study Poised for Success

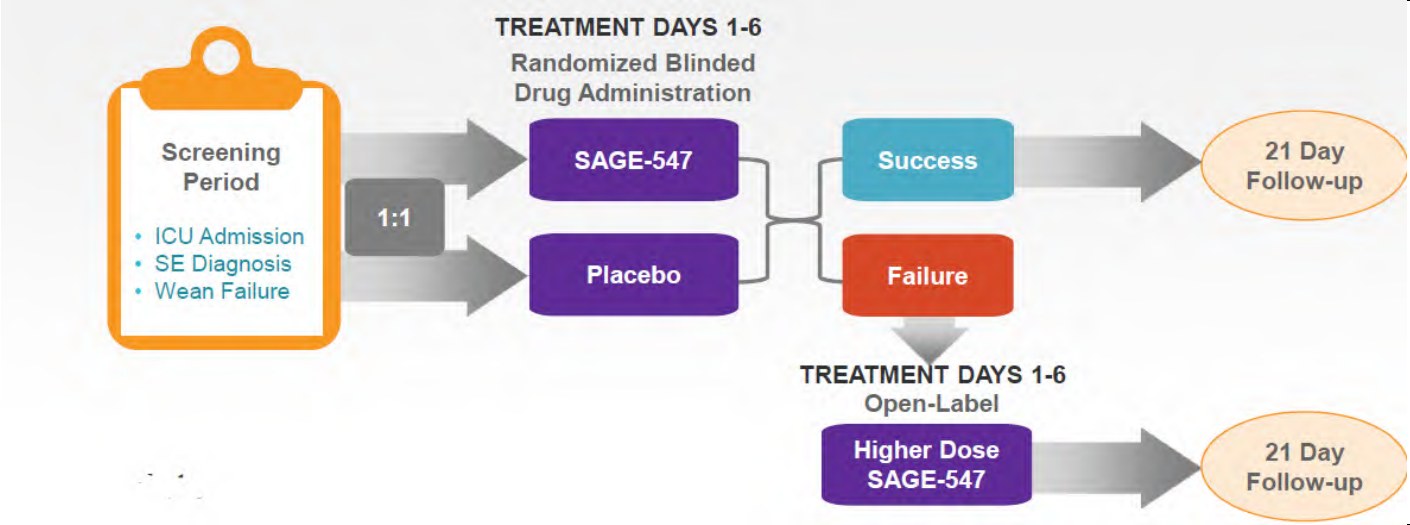
We see the upcoming Phase 3 pivotal STATUS trial as an important milestone and proof of concept for SAGE's GABA modulation platform. The trial will enroll 126 patients over the age of 2 at up to 150 sites in the US and Europe. Inclusion and exclusion criteria are identical to the Phase 1/2 trial, including the key anoxia exclusion criteria. Patients will be randomized 1:1 to '547 or standard of care third-line anti-seizure agents and placebo. Patients who don't respond to the initial blinded treatment may be eligible for an open label, higher dose retreatment regimen.

The primary endpoint is successful resolution of SE after weaning all third line agents and placebo without resumption of SE within 24 hours after '547 and or placebo. Secondary endpoints are rate of recovery, regaining of consciousness, mental status, and functional outcome.

The study is 90% powered to show an improvement in responder rate compared to an assumed 35% placebo response rate. Sage has not publicly released what percent increase in response rate the trial is powered to detect. We think even an absolute increase of 10% would drive significant use of the drug in SRSE. Enrollment is expected mid 2015, following submission review by FDA of the final trial protocol and CMC. While Sage has not commented on final data timing, we expect late 2016 or earlier topline data. Sage does expect the trial to allow for a 2017 NDA filing.

Based on the strong and consistent response rate seen in the Phase 1/2 study and the conservative assumption of the Phase 3 study, we and our consultants are optimistic for approval. We think that SAGE may be able to file for FDA and EMA approval on one Phase 3 trial, if effective. '547 already has orphan designation and fast-track status for SRSE.

SAGE-547 SRSE Phase 3 Trial Design



Source: Sage

Our physicians think that any statistical improvement over placebo (even one as small as 10%) would be sufficient for them to incorporate '547 into their practice, especially given positive safety data.

We think Sage's early relationships with the 150 clinical trial sites that likely treat a large share of SRSE patients could be beneficial for marketing efforts, if approved. Given that most patients are treated in a cluster of about 900 hospitals in the US, a focus on high-prescribing sites would contribute to significant uptake of '547, especially if physicians notice positive results with '547 treated patients in the trials.

Concerns

Scientific literature suggests SE patients with certain etiologies are more likely to experience positive outcomes than others. SAGE, however, is enrolling SRSE patients of any etiology in the Phase 3 trial, which could introduce enough variability to handicap success.

However, according to our consultants, etiology is less important in SRSE than in first-line SE, and Sage believes the size of the trial will compensate for any remaining confounding. Importantly, the Phase 3, like the Phase 2 will not include patients with anoxia, which we believe is a positive as these patients are frequently associated with worse outcomes. We do not think FDA would limit the label because their Phase 3 will still include patients of all etiologies.

SAGE disclosed that it would be using a different formulation for '547 in the Phase 3 trial than was used in the Phase 1/2 trial. The changes included several proprietary improvements in the product formulation that could conform to an IP advantage but should not impact the molecule itself. FDA will not require Sage to perform a bridging study as a result of these changes because there was no modification of the active pharmaceutical ingredient (API).

Potential Market

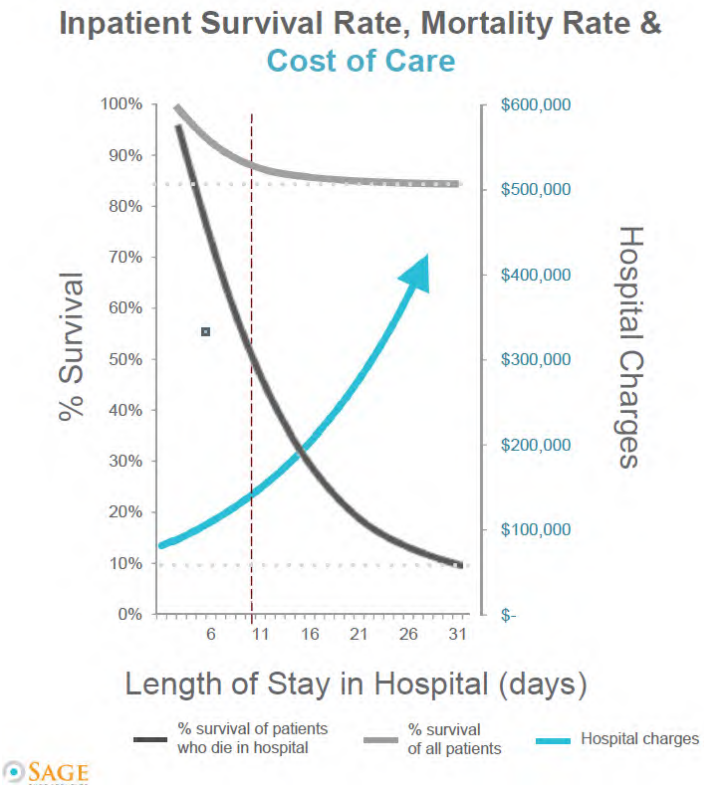
We model peak sales of SAGE-547 at $856MM in the US and $221MM in the EU. We model 75% and 60% market share in the US and the EU. SAGE can charge orphan pricing and build a streamlined salesforce to bring SAGE-547 to physicians and patients. About 900 US hospitals are responsible for 70% of SRSE discharges, enabling SAGE to train and use a relatively small salesforce.

Patients with SRSE are easily identifiable and present in the ICUs. We think there is no real competition, especially given the negative side effects and harms associated with prolonged anesthesia use.

We think that, if approved, physicians may decide to use '547 concurrent with first anesthesia treatment to improve odds of success upon first wean attempt. This should improve patient outcomes, especially functional morbidity.

If SAGE-547 proves to resolve epilepsy without anesthesia and could shorten the duration of SRSE, overall mortality as well as morbidity and out-patient recovery times and burdens could be reduced. This would be preferable to payors, as longer hospital stays are associated with higher costs and higher mortality/morbidity. The majority of patients who die do so within 9 days and are normally in an ICU setting. Given the high costs of ICU care (>$7-10k/day), we think payors would not contest a 20%-30% premium to available therapies that are used to treat SRSE patients (most of which do not work). As such we think a ~$60K/treatment course cost of '547 would be easily justified.

Length of ICU Care Associated with Higher Cost and Mortality



Source: Cowen and Company

Further, if '547 is approved in SRSE and the positive safety trend continues, we suspect physicians would use it in their RSE patients before giving them anesthesia. Additionally, given the mixed bag of SRSE definitions, physicians may be able to provide drug to an RSE patient under the mixed definition of SRSE.

SAGE-547 Market Model

US SRSE		2016	2017	2018	2019	2020	2021	2022	2023	2024	2025
SRSE											
# of SE cases (US)	*1%*	150,000	151,500	153,015	154,545	156,091	157,652	159,228	160,820	162,429	164,053
# of RSE cases (US)	*30%*	45,000	45,450	45,905	46,364	46,827	47,295	47,768	48,246	48,729	49,216
# of SRSE cases (US	*50%*	22,500	22,725	22,952	23,182	23,414	23,648	23,884	24,123	24,364	24,608
patients amenable			*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*
Penetration			*0%*	*10%*	*40%*	*60%*	*75%*	*75%*	*75%*	*75%*	*75%*
Patients on 547			0	1607	6491	9834	12415	12539	12665	12791	12919
Price	*2%*	$	$ 60,000	$ 61,200	$ 62,424	$ 63,672	$ 64,946	$ 66,245	$ 67,570	$ 68,921	$ 70,300
SRSE 547 Revenues (MM)		**$**	**$ -**	**$ 98.33**	**$ 405.19**	**$ 626.14**	**$ 806.31**	**$ 830.66**	**$ 855.74**	**$ 881.59**	**$ 908.21**
EU Top 5 SRSE											
# of SE cases (EU)	*1%*	75,000	75,750	76,508	77,273	78,045	78,826	79,614	80,410	81,214	82,026
# RSE cases (EU)	*37%*	27,750	28,028	28,308	28,591	28,877	29,166	29,457	29,752	30,049	30,350
# SRSE cases (EU)	*50%*	13,875	14,014	14,154	14,295	14,438	14,583	14,729	14,876	15,025	15,175
Patients amenable			*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*
Penetration			*0%*	*0%*	*10%*	*40%*	*60%*	*60%*	*60%*	*60%*	*60%*
Patients on 547			0	0	1001	4043	6,125	6,186	6,248	6,310	6,373
Price		$	$ 45,000	$ 35,000	$ 35,000	$ 35,000	$ 35,000	$ 35,000	$ 35,000	$ 35,000	$ 35,000
SRSE 547 EU Revenues ($MM)		**$**	**$ -**	**$ -**	**$ 35.0**	**$ 141.5**	**$ 214.4**	**$ 216.5**	**$ 218.7**	**$ 220.9**	**$ 223.1**
Total SRSE Revenues ($MM)		**$**	**$ -**	**$ 98.3**	**$ 440.2**	**$ 767.6**	**$ 1,020.7**	**$ 1,047.2**	**$ 1,074.4**	**$ 1,102.4**	**$ 1,131.3**

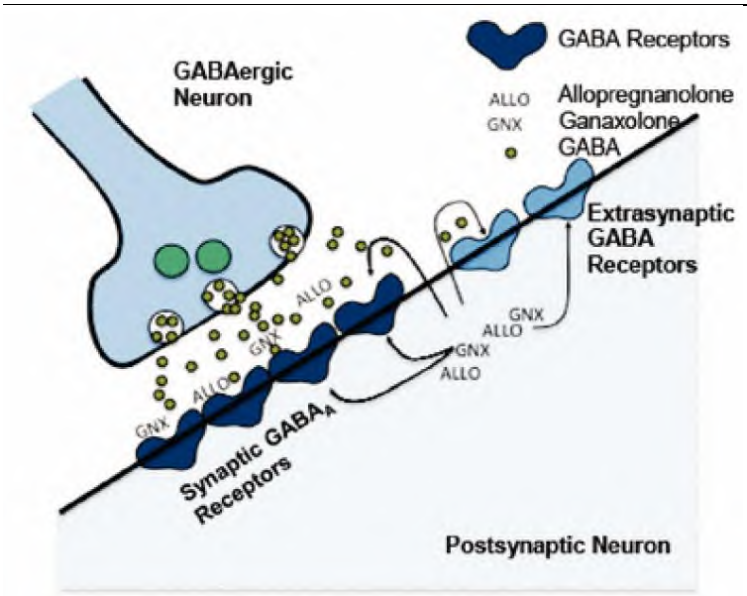
Source: Cowen and Company

Competition

Antiepileptic drugs are used in patients with SE to control seizures. The most commonly used generics are levetirectam, lamotrigine, carbamazepine, oxacarbazepine, valproic acid, and topiramate. Vimpat, Potiga, Fymcopa, and Aptiom have recently entered the anti-epileptic market. Brivarecetam and carisbamate are also in later stage clinical trials.

Marinus Pharmaceuticals is developing ganaxolone, a synthetic small molecule analog of allopregnanolone. Like allopregnanolone, Ganaxolone binds to the extrasynaptic receptor, but without the chronic-use side effects associated with allopregnanolone (we note that use of '547 in SRSE would be on a short-term acute basis).

Ganaxolone Mechanism of Action



Source: Marinus 10-K

Data from the ganaxolone Phase 2 trial in 147 patients with refractory focal onset seizures showed that adding ganaxolone to standard of care treatment reduced seizures by 26% (vs placebo 10.2%). The drug is also being evaluated in PCDH19 female pediatric epilepsy (an orphan indication), acute seizure treatment in hospitalized patients, and for behaviors in fragile X syndrome. Ganaxolone can be administered in an oral solid or liquid suspension dose form and is under investigation for IV delivery.

Phase 3 focal onset data will be presented in 1Q16 and PCDH19 data will likely produce initial data in 2015.

We do not see Marinus as significant competition because as the company only focuses, at this point, primarily on focal seizures and not status epilepticus, RSE or SRSE. We think that it may, at a later stage, be a competitor to SAGE's other compounds, especially given the similarity in mechanism. At this point, we see a symbiotic relationship between the two companies as more awareness around unique modulation of the GABA-A receptor could increase patient, physician, and investor confidence of the mechanism.

Other Indications

Sage is attempting to develop their GABA-A asset in other CNS disorders that could potentially be improved by the mechanism. Given already-established positive safety data, we see rapid pipeline expansion as highly likely. SAGE is pursuing well-defined indications that could potentiate rapid data read-outs. We expect data from ongoing essential tremor and postpartum depression exploratory studies in mid/early 2015.

Postpartum Depression is associated with low levels of allopregnanolone and affects up to 1M women in the US annually. PPD is characterized by irritable, severely depressed moods. Often, individuals afflicted with PPD experience crying spells, insomnia, depressed mood, fatigue, anxiety, and poor concentration. The majority of

factors associated with PPD are social in nature, and women with a history of depression are at a higher risk for developing PPD. PPD occurs in women within 4 weeks of giving birth, and as late as 30 weeks postpartum.

Most women are treated with psychotherapy and then, as needed, medication. Antidepressants, hormonal supplements, and omega-3 fatty acids are used for the prevention and treatment of PPD. The data on pharmacotherapy for PPD is quite thin. Nonetheless, serotonin reuptake inhibitors are considered first-line for women with PPD without Bipolar Disorder.

The GABA-ergic mechanism has been validated in PPD, and we think there is room in the treatment market for a new safe, entrant with a unique mechanism.

A Phase 2 trial evaluating SAGE-547 in 10 adult females with severe postpartum depression is currently underway. The open label proof-of-concept study primarily evaluates safety and tolerability. Secondary outcomes include PK and patient symptom responses (change from baseline in Hamilton Rating Scale for Depression-17, Clinical Global Impression-Improvement). Key inclusion criteria include adult females (18-45 yrs) who experienced a major depressive episode in the postpartum period within four weeks after delivery. Patients with active psychosis or a medical history of tumors are excluded.

Essential Tremor is linked to GABA receptor function and is the most prevalent tremor disorder. About 1.5M in the US have moderate-to-severe essential tremor (4% of individuals over 40). Clinical features of ET includes several motor features such as tremor and ataxia, as well as nonmotor features such as possible cognitive impairment and personality perturbances. Over 90% of ET patients seeking medical attention had reported disability. The most severe patients cannot perform basic tasks such as feeding or dressing themselves.

The pathology of ET is divided into patients with cerebellar degeneration and brainstem Lewy bodies. Patients with cerebellar degeneration show to have a large number of Bergmann glial cells and torpedoes compared to healthy patients. The tremor itself is likely mediated by a neuronal loop which involves cerebellothalamocortical fibers. Patients with the Lewy Body type of ET tend to have a unique pattern of lewy bodies in the brainstem. The patterns involved in ED are unique to those in Parkinson's patients, who are also impacted by abnormalities in Lewy Body abnormalities. Patients with ET can eventually develop PD.

The GABA hypothesis in ET assumes the disturbance in the GABA-ergic system is involved in ET in four steps.

1. Cerebellar degeneration and Purkinje cell loss

2. As a result of (1), activity of GABA decreases in deep cerebellar neurons

3. Pacemaker features of deep cerebellar neurons stops being inhibited

4. Tremor is caused by increased rhythmic activity of thalamus and thalamocortical circuit.

Drugs that enhance GABAergic transmission have shown efficacy in ET. Barbiturates, Primidone, and Alprazolam have been used to treat ET. Ethanol is often effective in reducing the severity of tremor because alcohol is an indirect GABA agonist. Given the established GABAergic mechanism in ET and '547's established safety profile, we

think '547, if approved in ET, could become a preferred treatment option for these patients.

A placebo-controlled, two-period crossover Phase 2 study is underway to evaluate '547 in 24 patients with ET. The primary endpoint is safety and tolerability. Secondary endpoints include the effect of '547 on patient response as measured by accelerometer, The Essential Tremor Rating Scale (TETRAS), and PK. Patients included in the trial are males and females, ages 35-75, with a diagnosis of essential tremor with symptoms clearly present in at least one upper limb. Patients included also had tremor present for at least two years prior to screening. Exclusion criteria include a medical history of seizures.

SAGE-689

SAGE-689 is in development as a 2nd-line adjuvant SE therapy. It has a similar GABA-A mechanism to that of '547 but has additional sedative properties. It is intended for use in patients for whom BDZ does not resolve seizure and is designed to treat SE in a second-line non-hospital setting. SE patients are transported to a hospital by ambulance and are often treated in the ER with anti-seizure drugs. They are moved to the ICU and placed in a medically induced coma if the seizure does not end. '689 is designed to treat a patient before placing him/her into a medically induced coma, which is preferable from an efficacy, risk, and safety perspective. '689 is being developed in IV and IM forms.

IND-enabling toxicology studies are underway, and Sage anticipates the filing of an IND in late 2015 with a Ph1 trial beginning shortly thereafter.

689 has a short half-life, allowing for physicians to control the amount of circulating drug and the duration of its effect. This is superior to other compounds such as anesthetics which have long half lives, which is seen as a negative feature for these patients because physicians cannot adjust dosing.

Trial History

In mouse models, a single IV bolus of SAGE-689 (5 mg/kg and 15 mg/kg) dosed up to 60 minutes following the onset of SE resulted in a complete halt of seizure activity. '689 also showed to effectively and dose-dependently stop the re-occurrence of seizures up to three hours after treatment. In the same rodent SE model, BDZs did not show effectiveness in seizure cessation.

In rats and dogs, '689 was shown to be a fast acting, reversible sedative/hypnotic agent. At low doses, '689 resulted in light sedation, but at higher doses, produced general anesthesia. Because of this dose dependence, '689 can produce varying levels of sedation that can be quickly reversed and is safe, especially compared to standard of care propofol. Recovery from sedation after the withdrawal of '689 was rapid, and in rats, occurred within 15 minutes after a 1 hour continuous IV was delivered.

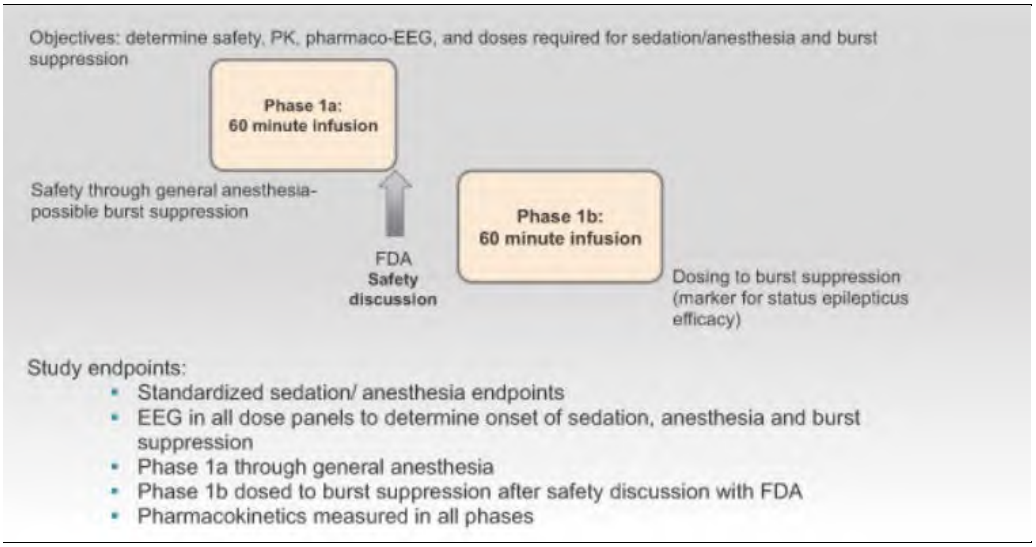
Telemetry studies showed that '689 had less severe cardiovascular and respiratory effects than propofol.

Phase 1 study

There is little detail on the planned Phase 1 '689 study. We expect an IND to be filed in late 2015. The Phase 1 program, which is expected to begin shortly after IND filing,

would assess quality of sedation, impact on EEG in normal patients and, possibly, those with epilepsy, PK, and general safety. The Phasem1 study will also guide Sage in determining whether '689 is best suited as an adjunctive therapy or monotherapy. We expect '689 to show a superior safety and slightly improved efficacy profile compared to standard of care.

SAGE-689 Phase 1 Trial Design



Source: SAGE

SAGE-217

IND enabling studies are ongoing for SAGE-217, which is being developed as an oral monotherapy for orphan epilepsies, such as Dravet and Rett Syndrome, described below. It was initially developed as an IV monotherapy in RSE, with the potential to prevent recurrent seizures in a broader epilepsy population as well as orphan genetic seizure disorders. '217 could potentially be formulated as an IV, oral, or PO medication for Dravet and Rett syndromes. Sage plans to file an IND by late 2015 and to begin a Ph1 trial shortly thereafter. We do not include SAGE-217 in our valuation because it is still too early to assign specific value to the program.

SAGE-217 was designed to induce deep anesthesia and confirmed EEG burst suppression. The long half-life allows for an auto-taper on cessation to avoid rapid fluctuations in blood levels

Orphan Epilepsies

Dravet Syndrome accounts for about 5% of childhood epilepsy that presents in the first year of life. About 5,440 and 6,700 children in the US and EU have Dravets. Severe Myoclonic Epilepsy in Infancy. One of the most severe epileptic encephalopathies and one of the best understood. 70-80% of Dravet cases are linked to the alpha sodium channel subunit (SCN1A) gene. Mild mutations in the gene do cause a benign form of epilepsy, while mutations to the gene impair function of the protein responsible for Dravets. Alterations in other genes, notably GABRG2 and PCDH19 are also associated with the syndrome, but to a lesser extent (3% of cases).

Core features of Dravets are onset of febrile or afebrile seizures in the first year of life in a previously normal child. The initial seizures are hemiclonic (limited to one side of the body) or tonic clonic, but subsequently patients experience a variety of seizure types that become intractable. Dravet is considered incurable because patients fail to respond to the AEDs that are currently available.

Proper management can provide significant seizure relief, but Dravets patients do indeed develop cognitive impairment. About half of Dravet patients will have adequate response to AEDs. Physicians have reported relatively positive experience with stiripentol, especially in combination with valproate and/or clobazam.

Rett Syndrome is a neurodevelopmental disorder that affects females. The MECP2 mutation is the most common form, but the CDKL5 mutation most significantly affects the early onset seizure variant. Rett's is the second most common form of severe mental retardation in females after Downs Syndrome and affects about 1 in 10,000 females (about 16,000 in the US). The disorder is characterized by a progressive loss of intellectual function, fine and gross motor skills and communicative abilities, deceleration of head growth, and the development of stereotypic hand movements. Symptoms appear after a period of normal development in the first 5-6 months.

Girls with Rett's often develop seizures, disturbed breathing patterns, scoliosis, growth retardation, and gait apraxia. About 90% of Rett's patients experience epilepsy, mostly after the age of 2. The seizures are not limited to one type and include tonic-clonic, absences, myoclonic, tonic, and focal seizures. The epilepsy symptoms are usually treated with valproate, lamotrigine, carbamazepine, and clobazam. About 56% of patients achieve remission from epilepsy after one therapy, and 18% after a second. However, patients can experience adverse events that can be exacerbated by their preexisting condition (motor problems, tremor, sedation, irritability, decreased alertness and communication).

Competition

GWPH's Epidiolex is in later stage clinical development (Phase 3 study has been initiated) and has shown promising results in intractable forms of epilepsy such as Dravet's and Lennox Gastaut. Epidiolex is an oral liquid formulation of a highly purified extract of CBD (cannabidiol) and is poised to present initial data in these indications by year-end 2015. We therefore see more of an opportunity in Rett Syndrome, given the lack of treatment options in development. Nonetheless, given that '217 and Epidiolex operate via different mechanisms of action, the two should be able to be used in combination if deemed appropriate by a physician.

Clinical Trial History

Animal models showed that '217 was pharmacologically active in different seizure models. In rodents, '217 produced complete cessation at 3 mg/kg and 5 mg/kg IV infusions. '217 effectively halted seizure recurrence for up to three hours after treatment initiation.

'217 had low systemic clearance and a long half-life in rodents and dogs. It was also shown to cross the blood brain barrier effectively with brain to plasma ratio >1.

Intellectual Property

Allopregnanolone is an endogenous molecule and is therefore not covered by composition of matter IP. SAGE-689, SAGE-217 and future NMDA products are NCEs (new chemical entities), which will likely be able to be covered by composition of matter patents. Sage's IP portfolio can be divided into three groups.

1. **SAGE-547:** SAGE models ~7.5 years of IP protection under the orphan and pediatric exclusivity in the US and ~10 years of data exclusivity in the EU. SAGE has claims to the formulation (allopregnanolone+cyclodextrini) and claims directed to methods of treating seizure disorders, including SE, by administering allopregnanolone using particular dose regimens and dose phases (exp 2033).

2. **SAGE-689:** This patent application is co-owned with WU. IP is directed to GABA receptor modulating compounds and methods of use. The '689 patent discloses and claims its use in anesthesia or the treatment of GABA-related disorders (exp December 2033). Another patent, (7,781,421) is owned by WU (exp 2027). There are an additional 5 patents owned by WU that expire 2032-2034.

3. **SAGE-217 and NMDA Receptors:** SAGE has patent families around '217. SAGE also owns 3 families of applications directed to NMDA modulators. 2 of these are directed to compounds that modulate the NMDA receptors. The other is directed to using a naturally occurring compound as a biomarker for a subject who could benefit from treatment of an NMDA modulator. This IP family expires 2032-2034.

Valuation Methodology And Risks

Valuation Methodology

Biotechnology:

In calculating our 12-month target price, we employ one or more valuation methodologies, which include a discounted earnings analysis, discounted cash flow analysis, net present value analysis and/or a comparable company analysis. These analyses may or may not require the use of objective measures such as price-to-earnings or price-to-sales multiples as well as subjective measures such as discount rates.

We make investment recommendations on early stage (pre-commercial) biotechnology companies based upon an assessment of their technology, the probability of pipeline success, and the potential market opportunity in the event of success. However, because these companies lack traditional financial metrics, we do not believe there are any good methodologies for assigning a specific target price to such stocks.

Investment Risks

Biotechnology:

There are multiple risks that are inherent with an investment in the biotechnology sector. Beyond systemic risk, there is also clinical, regulatory, and commercial risk. Additionally, biotechnology companies require significant amounts of capital in order to develop their clinical programs. The capital-raising environment is always changing and there is risk that necessary capital to complete development may not be readily available.

Risks To The Price Target

SAGE's lead program has been successful in a Ph1/2 trial. This, however, does not guarantee success in future trials as well as success in trials for SAGE's follow-on compounds, '217 and '689. Clinical success does also not guarantee commercial success, and while we believe '547 can achieve $75K pricing and a 75% market share in the US, these are our projections and SAGE may not reach these sales figures.

Addendum

Stocks Mentioned In Important Disclosures

Ticker	Company Name
FOLD	Amicus Therapeutics
CEMP	Cempra
SAGE	Sage Therapeutics

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Cowen and Company, LLC. New York (646) 562-1000 **Boston** (617) 946-3700 **San Francisco** (415) 646-7200 **Chicago** (312) 577-2240 **Cleveland** (440) 331-3531 **Atlanta** (866) 544-7009 **London** (affiliate) 44-207-071-7500

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Underperform (3): Stock is expected to achieve a total negative return of at least 10% over the next 12 months

Assumption: The expected total return calculation includes anticipated dividend yield

Cowen and Company Rating System until May 25, 2013

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Assumptions: Time horizon is 12 months; S&P 500 is flat over forecast period

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Rating	Count	Ratings Distribution	Count	IB Services/Past 12 Months
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Sell (c)	15	1.96%	0	0.00%

(a) Corresponds to "Outperform" rated stocks as defined in Cowen and Company, LLC's rating definitions. (b) Corresponds to "Market Perform" as defined in Cowen and Company, LLC's ratings definitions. (c) Corresponds to "Underperform" as defined in Cowen and Company, LLC's ratings definitions.

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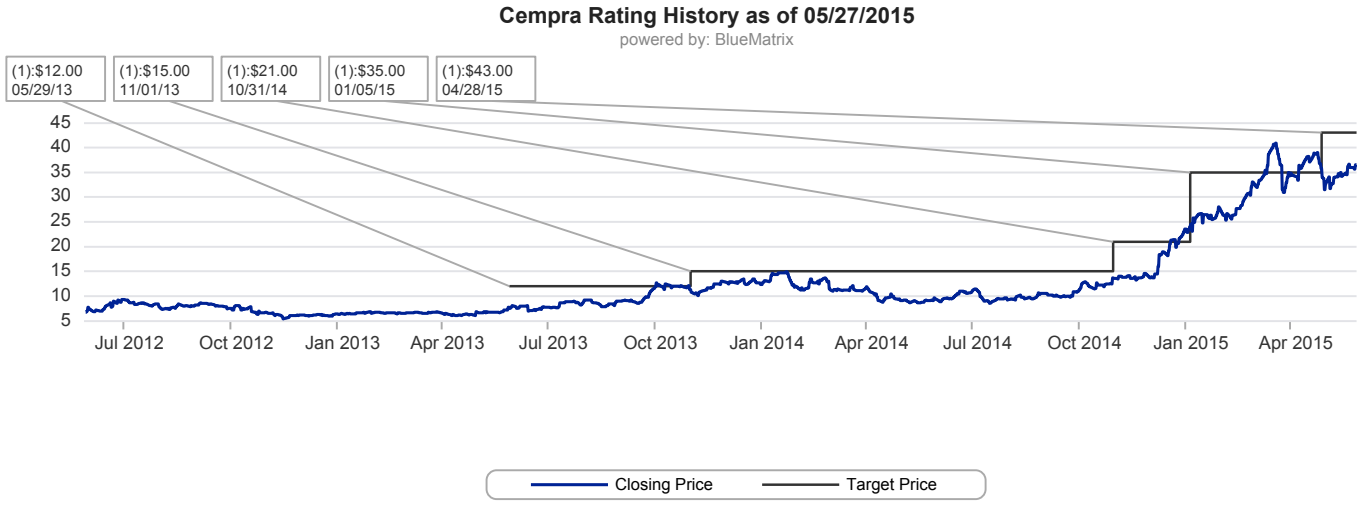

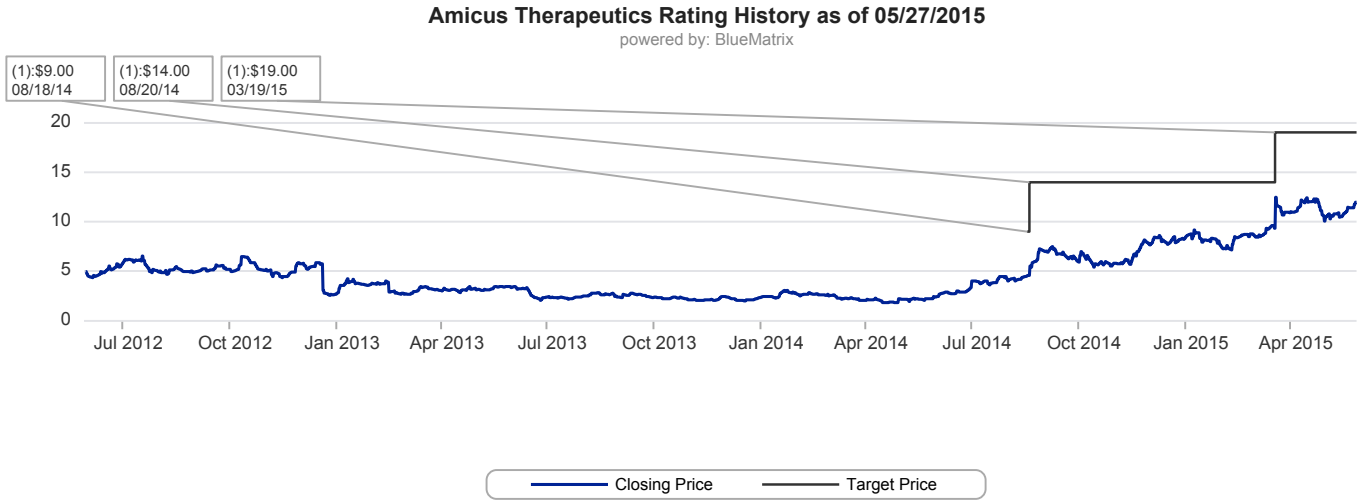

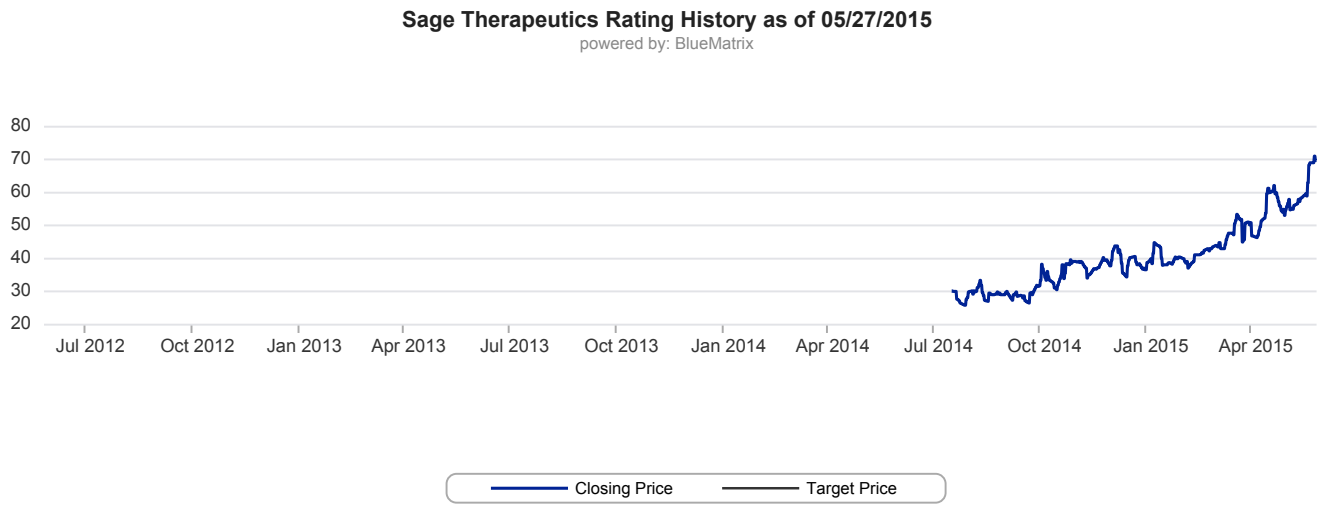

Legend for Price Chart:

I = Initiation | 1 = Outperform | 2 = Market Perform | 3 = Underperform | UR = Price Target Under Review | T = Terminated Coverage | $xx = Price Target | NA = Not Available | S=Suspended

Points Of Contact

Analyst Profiles

Ritu Baral
New York
646.562.1379
ritu.baral@cowen.com

Ritu Baral is a senior analyst covering the biotechnology sector. She joined Cowen in 2014, having previously worked at Canaccord.

Elyse Shapiro
New York
646.562.1426
elyse.shapiro@cowen.com

Elyse Shapiro is an associate covering the biotechnology sector. She joined Cowen in June 2014 from Canaccord Genuity.

Reaching Cowen

Main U.S. Locations

New York
599 Lexington Avenue
New York, NY 10022
646.562.1000
800.221.5616

Boston
Two International Place
Boston, MA 02110
617.946.3700
800.343.7068

Cleveland
20006 Detroit Road
Suite 100
Rocky River, OH 44116
440.331.3531

San Francisco
555 California Street, 5th Floor
San Francisco, CA 94104
415.646.7200
800.858.9316

Atlanta
3399 Peachtree Road NE
Suite 417
Atlanta, GA 30326
866.544.7009

Chicago
181 West Madison Street
Suite 3135
Chicago, IL 60602
312.577.2240

International Locations

Cowen International Limited

London
1 Snowden Street - 11th Floor
London EC2A 2DQ
United Kingdom
44.20.7071.7500

Cowen and Company (Asia) Limited

Hong Kong
Suite 1401 Henley Building
No. 5 Queens Road Central
Central, Hong Kong
852 3752 2333

@CowenResearch

Cowen and Company