SAGE Therapeutics, Inc. (SAGE)

The Rare CNS Play; Initiating with Buy and $67 PT

Initiate Buy

Price Target: $67.00

SAGE is positioning itself as a premier orphan play, focused on central nervous system (CNS) diseases of high unmet need, with well-defined molecular characteristics and likely short drug development timelines. We recommend owning shares ahead of clarity in Q1 on lead product 547 pivotal trial plans (mid-15 start) for super refractory status epilepticus (SRSE), drawing on highly compelling Phase I/II and emergency use data, and Phase II top-line data in two other indications in mid-15. In addition, two new products (689, 217) are expected to enter the clinic and the next program will be disclosed in late-15.

- **SAGE-547 could become the first standard of care (SoC) for SRSE.** 547 is a proprietary formulation of the naturally-ocurring neural molecule, allopregnanolone, which modulates the GABA brain receptor. Unlike GABA-binding agents currently used for seizure management, 547 binds both synaptic and extra-synaptic receptors. SAGE is evaluating 547 for SRSE - sustained epileptic seizures (>24hrs) in spite of treatment with several lines of currently available drugs, including general anesthesia. 12/17 (71%) evaluable SRSE patients in a Phase I/II trial and 78% (7/9) emergency use patients remained SE free for >24hrs post GA and 547 weaning.
- **Physicians highlight the unmet need for SRSE and view 547 response rates as encouraging.** Key opinion leaders cited the high mortality rates for SRSE (40%) and limited activity for available therapies (22-45%). They highlight the lack of a SoC for SRSE and note variability in type and sequence of anesthetics in different centers or within a single hospital. KOLs believe the ~71-78% response rates for 547 are “impressive”, given the lack of status epilepticus over 24 hours post weaning.
- **Key question is the 547 pivotal trial design and timeline.** SAGE will hold an End-of-Phase II meeting with the FDA in Q1/15, outcome to be disclosed thereafter. A pivotal trial of 100-200 patients, 1-2 years duration could entail either: 1) a single arm trial using historical efficacy data for comparison, or 2) a controlled-study using current SoC as comparator. We conservatively model for the latter assuming data in mid-17 (2-year study).
- **Pipeline advances and a busy 2015 should bode well for SAGE shares.** SAGE is using 547 as a "probe molecule" for essential tremor and post-partum depression, with 2 Phase II studies to read out in mid-15, to inform the design of a new agent. SAGE 689 and 217 will enter the clinic in late-15 for use in 2nd-line SE and an orphan CNS disease. An NMDA modulator program will likely be disclosed in late-15.
- **We estimate peak 547 WW sales of $1.7B in 2026.** We model for 22K, 35K, and 35K patients in the U.S., E.U., and ROW, peak penetration of 547 of 72%, 40%, and 9%, peak sales of $1B, $0.59B, and $0.1B in 2026 in the U.S., E.U., and ROW. We assume no contribution from preclinical assets SAGE 689 and SAGE 217.

Price (Jan. 23, 2015)	$38.25
52-Wk Range	$44.73-$25.86
Market Cap ($M)	$987
ADTV	101,317
Shares Out (M)	25.8
Short Interest Ratio/% Of Float	8.7%
TR to Target	75.2%

Cash Per Share	$4.38
Total Debt	$0.0
Cash And Equivalents ($M)	$136.7

	2014E	2015E		2016E	
		Curr.	Prior	Curr.	Prior
Revenue ($M)					
FY	0	0	--	0	--
EPS Adjusted					
FY	(2.50)	(2.28)	--	--	NA
P/E	NM	NM		--	
Consensus Rev					
FY	0	0	--	0	--
Consensus EPS Adjusted					
FY	(2.46)	(2.02)	--	(2.66)	--
FYE Dec					

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SEE PAGE 40 FOR REQUIRED DISCLOSURE INFORMATION

SAGE Bull/Base/Bear Scenarios

Figure 1: Bull/Bear Analysis for SAGE

	Bear Case	STRH case	Bull Case
SAGE-547 - U.S.	$9.87	$53.49	$64.55
SAGE-547 - E.U.	$1.06	$8.76	$18.68
SAGE-547 - ROW	$0.00	$0.62	$1.35
Cash/share	$4.38	$4.38	$4.38
Implied Price Target	**$15.31**	**$67.24**	**$88.97**
STRH est. scenario probability	10%	60%	30%
Price as of 01/23/2015		$38.25	
Upside/downside	*-60%*	*76%*	*133%*

Sources: Company reports, STRH research

Our base case: 60% probability. This valuation scenario reflects a 58% probability of success for SAGE's SAGE-547 (novel reformulation of allopregnanolone) for super refractory status epilepticus (SRSE) in the U.S., where encouraging Phase I/II and emergency use data have been gathered to date, and a 25% probability of clinical and commercial success in the E.U. and in the rest of the world (ROW). Given the promising nature of these data and optimistic view of our physician consultants, we assign a 60% probability to this scenario. Our base case does not include any revenue contributions or value for the two preclinical pipeline programs SAGE-217 and SAGE-689. These assumptions translate into a target of $67, 76% higher than the $38.25 closing price for SAGE shares on 01/23/15.

Our bear case: 10% probability. This valuation scenario assumes mixed results in an expected pivotal study of SAGE-547 in SRSE in the U.S., corresponding to a 25% probability of success. This scenario also assumes a longer development process for SAGE-547, a smaller commercialization window ahead of the product's IP expiration, and thus no terminal value for SAGE-547 in the U.S. The bear scenario assumes small chances of success in the E.U. and ROW, of 10% respectively. This scenario would translate into a price target of $15.31, 60% below the $38.25 closing price for SAGE shares on 01/23/15.

A bull case for SAGE: 30% probability. This valuation scenario would entail a 70% probability of success for SAGE-547 in SRSE in the U.S. based on promising results to date, and the FDA agreeing on the use of historical data as comparator for a pivotal trial. This scenario would also entail a 55% probability of success for SAGE-547 in SRSE in the E.U. and ROW, translating into a price target of $89, 133% higher than the $38.25 closing price for SAGE shares on 01/23/15. Notably, our bull case scenario does not ascribe any value to the two preclinical pipeline programs SAGE-217 and SAGE-689.

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We are Initiating Coverage of SAGE with a Buy Rating and $67 PT

SAGE is positioning itself to address orphan central nervous system (CNS) disorders with high unmet need. SAGE is one of the few players in the CNS space, a field with significant unmet need – that has been historically difficult to tackle in drug development. The company recently went public (IPO on 07/17/14, shares up 118% over the S1 offering price) with the key strategy to use its broad platform (chemical modulators of brain molecules) to focus on drug development for CNS indications that are: 1) well-defined from a molecular perspective, and 2) have short drug development timelines (small numbers of patients, short clinical trial duration). SAGE's lead drug candidate is SAGE-547, a modulator of the neural gamma-amino butyric acid (GABA) receptor. SAGE-547 is about to enter pivotal testing in mid-2015 for super-refractory status epilepticus, a rare type of epilepsy characterized by persistent seizures (>24 hours), in spite of treatment with multiple rounds of anesthetics. The company has two second generation molecules in the wings (SAGE-217 and SAGE-689) expected to enter the clinic in late-2015, as well as a platform of early stage modulators (N-Methyl-D-aspartic acid receptor, NMDA) of cellular brain function, slated to expand the epilepsy/CNS orphan disease franchise.

Results to date with SAGE-547 appear highly compelling compared to historical activity rates. SAGE-547 is a novel formulation of the naturally-occurring neural molecule allopregnanolone, formulated with cyclodextrin excipients (non-active drug substance) that allow for longer half-life and good bioavailability. The drug binds both synaptic and extra-synaptic GABA receptors, providing differentiation from standard of care benzodiazepines (BDZs), barbiturates, other anti-epileptic drugs (AEDs) such as phenytoin and levetiracetam, and general anesthetics that only bind synaptic GABA receptors. SAGE-547 has been studied in a Phase I/II study in 17 patients with SRSE who were given the drug intravenous for 5 day (days 1 and 2: SAGE-547+ general anesthetics (GA); day 3: SAGE-547 while tapering general anesthetics; day 4:SAGE-547 alone; day 5: taperingSAGE-547). 71% (12/17 patients) reached both efficacy endpoints of: 1) wean off general anesthetics while on SAGE-546, 2) remain status epilepticus-free for more than 24 hours after SAGE-547 weaning. These data are corroborated by activity in 78% (7/9 patients) treated under emergency use who remained SRSE for more than 24 hours after weaning of SAGE-547 and general anesthetics. These 70%+ response rates with SAGE-547 compare well with 43% and 22% response rates seen with standard of care propofol and barbiturates, respectively (Rosetti et al., 2011).

Physicians are enthusiastic on the potential of SAGE-547, highlighting the lack of a standard of care in SRSE. KOL neurologists we spoke with cited the high mortality rates associated with SRSE, of about ~40%, and expectations that less than a third of patients will return to a no-seizure baseline with weaning of medication. Physicians believe that the mechanism of action of SAGE-547 is well-suited for the drug's use in SRSE, given its ability to modulate both synaptic and extra-synaptic GABA receptors. Preclinical data

suggest that the higher the exposure to currently available GABA-targeted agents, the lower the availability of synaptic GABA receptors. The belief is thus that patients who fail multiple rounds of therapy harbor less available GABA receptor for modulation. Within a single center, physicians may choose to retain a patient under anesthetics. The current thinking is that SE may resolve itself, for some patients maintained under general anesthesia for a long time. However, this results in a high cost to the system for SRSE patients, who can remain in the hospital for months. KOLs also cite a limited understanding of whether prolonged medication or simply stochasticity cause the disease to resolve itself, leading to seizure cessation. However, SRSE patients that are successfully weaned off from AEDs have already been exposed to a slew of agents, thereby rendering it difficult to discern which one was active. Our KOL consultants note the difficulty of designing a well-controlled pivotal study, given the variability of treatments (choice and sequence of anesthetics) given at different centers or even within a single center. They do believe that a historical comparator would be appropriate, in their experience, in light of the narrow band of responses and survival rates in this patient population. They believe that a pivotal trial would be very easy to enroll once the typical number of cases per center per year is established. *"By the time patients reach SRSE, few of their legally-authorized representative would not agree to have a patient try a new medication".* Our consultants believe that the SAGE-547 results to date with ~71-78% response rate were "impressive", given the lack of status epilepticus over 24 hours post weaning.

SAGE outlined two potential scenarios for a SAGE-547 pivotal study design: 1) a single arm, historical control, and 2) a controlled cross-over study. The key question for SAGE relates to the design and timelines of the planned SAGE-547 pivotal study in SRSE (expected to start in mid-2015). The trial design details will be finalized after an End-of-Phase II meeting (Q1/15). The efficacy endpoint of the pivotal trial will likely be the proportion of patients to remain SRSE-free after tapering off SAGE-547 treatment (48 hour signal for acute efficacy and further follow-up for at least 14 days). Management expects a trial of 100-200 patients, to complete in 1-2 years. The first potential scenario entails a two-arm, controlled trial, with standard of care used as control. Patients failing to wean off general anesthetics in the control arm could cross over to the SAGE-547 arm. We believe that this study would likely require ~200 patients. Given that investigators can currently determine very rapidly if patients do not respond to SAGE-547 treatment, we believe a controlled-trial could be completed ahead of the higher end of the company's guidance of ~1-2 years. In the more conservative scenario, pivotal data could become available ~2 years after the anticipated mid-2015 start, in mid-2017. A single-arm pivotal study may allow for a smaller trial size and more rapid readout. Based on the 70%+ response rates seen to date with SAGE-547, SAGE believes institutional review boards (IRBs) at potential trial sites may oppose the use of a control arm. In this scenario, a single arm trial could support registration, with efficacy rates to be compared with historical responses. Such a study could require ~100 patients and its duration would likely be at the lower end of the company's 1-2 year time-to-completion guidance. In this scenario, pivotal data for SAGE-547 could be available

within 1 year from the mid-2015 expected study start, in mid-2016. SAGE-547 could therefore enter the market as early as mid-2017.

SAGE-547 could provide important proof of principle for essential tremor (ET) and post-partum depression (PPD). Two exploratory Phase II trials are currently ongoing in ET and PPD, with data expected in mid-2015. However, SAGE-547 is being used solely as a "probe" for ET and PPD, as the compound will not be developed "as is" for either of the two indications. An activity signal in these trials could enable the company to select one of the >1500 GABA-modulating candidate molecules in its pipeline to advance into the clinic. Early data from PPD and ET could enable the company to identify compounds with the appropriate oral dosing, PK and PD parameters, and correct biomodulation of the GABA target. Notably, an activity signal for could be assessed in each indication with minimal R&D spend given small clinical trials (24 patient study in ET and 10 patients in PPD). In ET, the rationale for GABA modulation stems from the fact that benzodiazepines (GABA modulators) have been successfully used to date to address disease symptoms. Strong evidence for the role of allopregnanolone in PPD comes from studies in humans (Nappi et al, 2001) showing statistically significant inverse correlations between blood levels of the hormone and scores on the Hamilton Rating Scale for Depression (lower allopregnanolone and PPD appear correlated). Additional studies in rodents (Evans et al. 2012) have shown that treatment with allopregnanolone can alleviate depression in some models of chronic stress.

A lean commercial infrastructure will likely be sufficient to target a majority of SRSE patients; SAGE could go it alone forSAGE-547 in the E.U. SAGE-547 may be relatively inexpensive to commercialize given that there are only ~200 specialized epilepsy centers in the U.S., and ~900 U.S. hospitals are responsible for >70% of all U.S. discharges. A concentrated base of KOL neurologists are involved in treating the disorder, and patients are readily identifiable as they are already hospitalized in medically-induced comas. SAGE is thus likely to commercialize their first product in the U.S. on a stand-alone basis. To address the comparable number of E.U. hospitals where SRSE patients are treated, we believe SAGE may go it alone based on management comments that a partnership is not actively being pursued. Follow-on molecules will also benefit from synergy with an existing sales force, and will likely require minimal additional operating expenses beyond the first commercial product.

We estimate peak WW revenue for SAGE-547 of $1.7B in 2026. Our projected revenue comes solely from lead asset SAGE-547. We estimate that 140K patients develop SE per year in the U.S., 206K in the broad E.U., and 206K in the addressable rest-of-the-world countries, with 22K, 35K, and 35K progressing to SRSE, respectively. We conservatively assume positive data from the pivotal trial mid-2017 (the higher end of the 1-2 years management guidance and pivotal trial start mid-2015), leading to approval and commercialization in mid-2018 in the U.S., mid-2019 in the E.U., and late-2019 in ROW. We assume that SAGE goes it alone for commercialization in the E.U., given management commentary suggesting they are not actively looking for a partnership – which we believe is the correct approach given the orphan nature of this indication (small patient numbers; known treatment location of patients). We note the high cost associated with hospital stays for SRSE patients, with a median survival rate of 11 days associated

with a ~140K cost (per SAGE analyses). Management guided that pricing for a round of SAGE-547 treatment could range between $25K and $75K. We conservatively assume $50K/patient, but note that therapies such as BMRN's Kuvan that address ~25-30K patients are priced at ~$100K per year and SAGE-547 is a fixed-duration therapy with a potentially transformative clinical benefit. We conservatively assume a 20% gross-to-net discount for hospital-negotiated rates. We model for peak penetration of 72% in the U.S. (slight uptick from 70% in 2025 when Orphan Drug exclusivity ends), 40% in the E.U., and 9% in ROW in 2026. We forecast peak SAGE-547 revenue of $955M in the U.S. in 2026 based on SRSE sales alone (we conservatively do not assume any off-label use of SAGE-547 in earlier lines of status epilepticus therapy); peak E.U. sales of $590M in 2026 and peak ROW sales of $134M. We also do not currently model for sales from proof of concept indications ET and PPD, as well as other pipeline assets, and note that they provide upside to our model.

Pipeline assets SAGE-689 and SAGE-217 are likely to extend the epilepsy franchise and diversify into other orphan genetic disorders. SAGE's two follow-on assets have different pharmacokinetics than SAGE-547 and could be suited for other indications. SAGE-689 is an intravenous compound with a shorter half-life than SAGE-547. Its broad therapeutic index could enable physicians to control the level of sedation and allow for rapid drug clearance if required for earlier hospital discharge or transfer to the ICU for change in medication without residual drug remaining. SAGE-217 has a longer half-life to enable convenient once-daily oral dosing. Beyond SE, SAGE is expected to nominate a product for another orphan genetic seizure indication in 2015, likely the NMDA-targeted compound.

SAGE has the resources to take several shots on goal. We do not project any revenue for SAGE until 2018, at which time we assume SAGE-547 approval (conservatively model for a 2-year trial at the high end of management guidance of 1-2 years) for SRSE in the U.S. and forecast revenue of $63.8M, $332.8M, and $545.5M for 2018, 2019, and 2010, respectively. We model for a continuing ramp-up in quarterly expense in 2015 and 2016, as the pivotal trial of SAGE-547 begins in mid-2015 and novel products move into the clinic in late-2015 and 2016. We forecast that the company will achieve profitability in 2019. The company raised $94M with its initial public offering in July 2014, and shares are up 118% over the S1 price based on the 01/23/15 closing price. We believe SAGE has a cash runway into 2016, and we model for two follow-on equity offerings to support continuing activities: 1) an equity offering of ~2.857M shares at $70/share in early 2016, and 2) an equity offering of ~1.66M shares at $120/share in mid-2017, after a potential data readout from the SAGE-547 pivotal study.

Valuation

We arrive at our price target of $67 by means of a sum-of-the-parts discounted cash flow analysis, which ascribes $53.49/share to SAGE-547 U.S. sales, $8.76 to SAGE-547 E.U. sales, $0.62 to SAGE-547 ROW sales, and $4.38/share to cash. We assign SAGE-547 in a probability of success of 58% in the U.S., 25% in the E.U., and 25% in ROW. We assume a discount rate of 12% and a 1% terminal growth rate to SAGE-547 in the U.S. and the E.U., and no terminal value for SAGE-547 in ROW.

Investment Risks

The primary investment risks for SAGE include the following:

- **Clinical Risk:** SAGE-547 may fail to repeat its 71-78% response rate from Phase II trials and eIND use in the pivotal trial. It is possible that both the Phase II and emergency use patients had a higher chance of recovering from SRSE than the ~20-40% probability as reflected by literature, and the 30-50% chance quoted by our physician consultants. This could be due to the inclusion/exclusion criteria used in Phase II, or another reason altogether. Although the preclinical rationale for SAGE-547 is suggestive that the compound could have utility in ET and PPD, the benefit in animals may not translate well in humans. Finally, although they have similar putative mechanisms of action, there remains the risk that proof-of-concept for SAGE-547 does not read through to other GABA modulators SAGE-689 and SAGE-217.

- **Regulatory risk:** The FDA may require more rigorous clinical trials than we anticipate. We believe that SAGE's expected pivotal endpoint of being seizure-free after the patient is weaned from both general anesthesia and SAGE-547 should be appropriate. However, the FDA may ask for a randomized controlled study, which may be difficult to set up given the variability in standard of care among different treatment centers. Longer term follow-up could be required, for example an endpoint such as proportion of patients who are seizure free 1 month after wean. We expect clarity on this endpoint in Q1 2015, when SAGE communicates the results of their end-of-Phase II meeting with FDA.

- **Commercial risk:** SAGE plans to target the relatively small number of ICUs (~900 hospitals in the U.S.) and epilepsy treatment centers (~200 in the U.S.), where SRSE patients are treated. E.U. has a comparable number of centers. The remains a commercial risk (albeit low) that SAGE is unable to effectively reach these patients.

- **Competitive Risk:** Although we are not aware of any significant competitive drugs in development for status epilepticus (SE), Marinus Pharmaceuticals (MRNS) is developing ganaxolone, a similar GABA-receptor targeted agent (although restricted to hitting the synaptic receptors), for the treatment of other forms of epilepsy and Fragile X syndrome. Although ganaxolone is unlikely to be approved for SE without clinical trials in that population, if the drug does become available it could be used off-label.

- **Financial risk:** Given the expenses associated with conducting clinical trials and launch of the product, we anticipate that SAGE may have to issue additional equity through follow-on offerings.

CNS-Focused Pipeline with Near Term Catalysts

SAGE is focused on the clinical development of therapeutics for rare central nervous system (CNS) disorders.

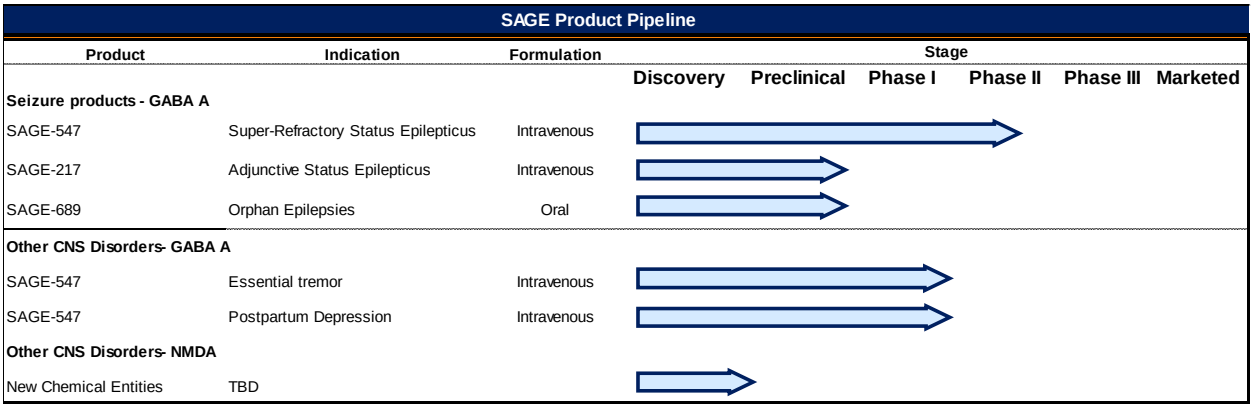
The company's first potential product, SAGE-547, is a proprietary intravenous formulation of the naturally-occurring neural molecule, allopregnanolone (produced from the hormone progesterone by the human brain and known to have sedative activity), for super refractory status epilepticus (SRSE), a type of epilepsy characterized by persistent seizures, in spite of treatment with multiple rounds of anesthetics. Allopregnanolone is a potentiator (i.e. positive modulator – akin to a thermostat vs. an on-off switch) of the neuronal receptor gamma-amino butyric acid (GABA) receptor, which functions to inhibit neural activity, yielding sedative effects. SAGE-547 has demonstrated promising activity in a Phase I/II trial; we expect a pivotal to begin in mid-2015 post end-of-phase II discussions with the FDA in Q1 (meeting outcome likely to be disclosed in Q1). Beyond SRSE, SAGE-547 is in two exploratory proof-of-concept Phase II trials for essential tremor (ET) and post-partum depression (PPD). However, SAGE does not intend to developSAGE-547 in either of these indications; instead activity in ET or PPD will likely inform future investigation of follow-on molecules.

SAGE's two follow-on programs, SAGE-689 and SAGE-217, are novel GABA-A potentiators. SAGE-689 has a shorter half-life than SAGE-547 and a wide therapeutic window which may enable a physician to more accurately dial up or down a patient's level of sedation. Physicians could use SAGE-689 to rapidly treat status epilepticus (SE) to avoid ICU admission. Given its clean drug-drug interaction profile, SAGE-689 could provide add-on benefit to the current standard of care. The product will enter the clinic in late-2015.

SAGE-217 has a long half-life to enable convenient, oral, once daily dosing. The product could be suited to intravenous dosing and it appears to have robust anti-seizure properties. SAGE-217 is slated to begin Phase I testing in late 2015, in an orphan genetic seizure disorder yet to be disclosed.

The next clinical candidate will be disclosed in late 2015. This will likely be a novel modulator of the neural N-Methyl-D-aspartic acid (NMDA) receptor (whose activation typically results in neuronal stimulation).

Figure 2: SAGE's Pipeline



Sources: Company reports, STRH research

Figure 3: SAGE Upcoming Milestones

Product	Timing	Indication	Event
SAGE-547	Q1 2015	Super refractory status epilepticus (IV)	End-of-Phase II (EOP2) meeting with the FDA
SAGE-547	Q1 2015	Super refractory status epilepticus (IV)	Announce EOP2 meeting outcome
SAGE-547	**Mid-2015**	**Post-partum Depression**	**Phase II topline data**
SAGE-547	**Mid-2015**	**Essential Tremor**	**Phase II topline data**
SAGE-547	Mid-2015	Super refractory status epilepticus (IV)	Initiate pivotal trial
SAGE-689	Late-2015	**Adjunctive Status Epilepticus (IV)**	Initiate Phase I testing
SAGE-217	Late-2015	Orphan Genetic Seizure Disorders (oral)	Initiate Phase I testing
NMDA modulator	Late-2015	Undisclosed orphan indication	Announce next program

Sources: Company reports, STRH research

SAGE is One of the Few Players in Orphan Central Nervous System Disorders

SAGE's focus is on developing therapies for rare CNS disorders with high unmet need. The company is led by an experienced management team with deep experience across multiple functions in chemistry, biology, clinical development, and commercialization. SAGE's value proposition resides with its platform of novel compounds for specific neural receptor modulation. The company's initial strategy is to explore indications whereby there is solid scientific rationale regarding modulation of the neuronal target GABA-A. Establishing an activity signal in these indications requires small clinical studies (~10-25 patients), a short period from enrollment to endpoint measurement, and a clear cut assessment of drug activity.

The company is initially pursuing a pipeline of molecules that positively modulate, or potentiate neural GABA receptors, which typically act to inhibit neural activity. Thus, dialing up GABA receptor activity could have utility in diseases whereby neurons fire abnormally (e.g. in case of seizures). GABA is also the target of several approved generic drugs including benzodiazepines, barbiturates, and some general anesthetics. However, the anti-seizure activity of these agents is typically restricted to synaptic GABA receptors (at the neuronal junction or synapse). Prolonged administration of these agents leads to decline of synaptic GABA receptor levels, even though seizures may continue. Extrasynaptic GABA receptors are not impacted by these drugs. In contrast, the naturally-occurring neural molecule allopregnanolone can modulate both intra- and extra-synaptic GABA receptors. SAGE-547, the company's proprietary formulation of allopregnanolone, could therefore provide additional benefit to benzodiazepines, barbiturates, and other anesthetics.

The first indication is super-refractory status epilepticus (SRSE), described in detail below. SAGE has also indicated it has plans to pursue potentiators of the excitatory NMDA receptors for rare monogenic CNS disorders in the near future.

SAGE-547: Acute Reset for Super Refractory Status Epilepticus

SAGE-547 is a proprietary formulation of a naturally-occurring molecule, allopregnanolone, with demonstrated efficacy in many mouse models. Allopregnanolone is produced by the human brain from the hormone progesterone, and its anti-convulsant (anti-seizure) activity has been well-described in preclinical models. One of allopregnanolone's key properties is its ability to modulate both synaptic and extra-synaptic GABA receptors. In addition, the molecule binds GABA at sites that are different from other GABA-targeted molecules, such as benzodiazepines and barbiturates. Unfortunately, the bioavailability of allopregnanolone is poor, thereby limiting the product's pharmacokinetic utility. SAGE-547 entails a proprietary formulation of

allopregnanolone, including a non-active drug ingredient called Captisol (a type of sugar, beta-cyclodextrin). This formulation prolongs the drug's half-life and appears to enable brain penetration, as demonstrated by preclinical data as well as clinical results generated to date. Indeed, initial data on intravenous-delivered SAGE-547 has been highly promising with respect to safety and efficacy. We discuss both the patients treated in an emergency use program (emergency investigational new drug program, eIND), as well as Phase I/II results below.

Unprecedented Responses of SAGE-547 in a Phase I/II study and a Group of Emergency Use Patients

The open-label Phase I/II trial is assessing SAGE-547 as adjunctive therapy to standard of care agents. An open label Phase I/II study of SAGE-547 dosed intravenous has been enrolling (20 patients as of 01/09/15) super-refractory status epilepticus (SRSE) patients since Jan 2014. The primary endpoint was safety and tolerability, while a secondary endpoint of efficacy evaluated: 1) the percentage of patients who achieved resolution of status epilepticus while on SAGE-547 but weaned off general anesthetics (Figure 4) and 2) the percentage of patients who remained status epilepticus-free after tapering 549.

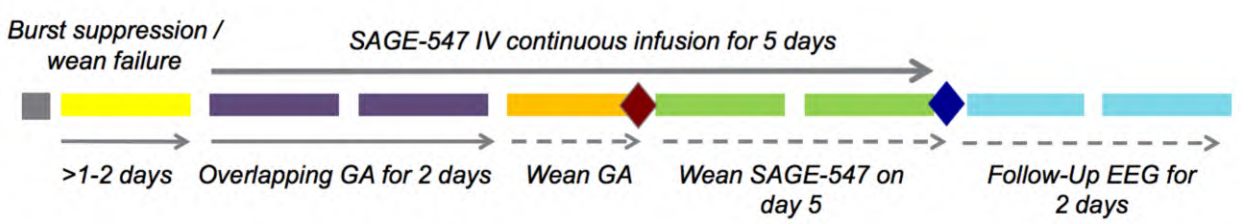
SAGE-547 was administered in addition to standard of care, which includes benzodiazepines, barbiturates, other anti-epileptic drugs (AEDs) with different mechanisms of action such as levetiracetam and phenytoin, and general anesthetics such as propofol. The study enrolled SRSE patients who were concurrently on a continuous IV anti-epileptic drug for more than 24 hours. The definition of SRSE must have included the following:

- Failure to respond to at least 1 first-line agent, such as a benzodiazepines
- Failure to respond to at least 1 second-line agent such as phenytoin, fosphenytoin, valproate, phenobarbital, or levetiracetam.
- Occurrence of at least 1 breakthrough seizure more than 6 hours after initiation of third-line continuous IV AEDs such as pentobarbital, midazolam, or propofol.

Patients under burst suppression with continuous intravenous AEDs were given an initial loading infusion of SAGE-547 over the course of 1 hour, followed by maintenance infusion for 96 hours (Figure 4). Post 48 hours on SAGE-547, patients were weaned from their general anesthetic agent, but allowed to continue on non-anesthetic AEDs (e.g. benzodiazepines, phenytoin, levetiracetam etc.). After the full 96 hours on SAGE-547, the study drug was tapered and discontinued (patient was "weaned" from drug). The % of patients who remained SE free 48 hours after SAGE-547 weaning was then assessed.

Management noted that investigators had sufficient flexibility with their choice of standard of care therapy.

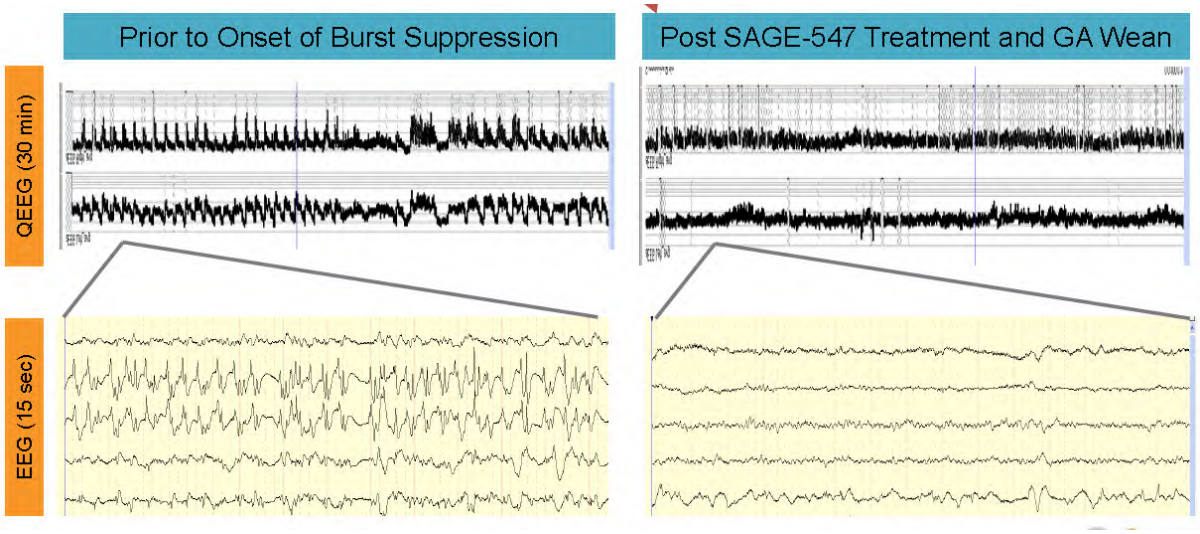
Figure 4: The Phase I/II Study Evaluated the Resolution of Status Epilepticus while on SAGE-547 and Post SAGE-547 Tapering



Sources: Company reports

Initial data showcased 73% responses, namely patients who were SE-free after weaning off both standard of care and SAGE-547. SAGE presented initial data from this study from 11 evaluable patients. 8/11 (73%) were successfully weaned off general anesthesia after 48 hours of concurrent SAGE-547 dosing without experiencing SE. Importantly, these 8 patients (73%) also remained SE-free for more than 24 hours after SAGE-547 tapering. There were no drug-related adverse events noted in any of the 12 patients enrolled. The mean SAGE-547 exposure was 200nM, suggestive of acceptable bioavailability. Furthermore, the mean duration of SE prior to dosing with SAGE-547 was 11 days (range 3-21). This previous long duration of SE is suggestive of a non-random effect of SAGE-547 dosing on top of the current standard of care and likely robust activity in light of maintenance of SE-free status for more than 24 hours.

Figure 5: SAGE-547 Demonstrated EEG Normalization that was Maintained Post-Wean



Sources: Company reports

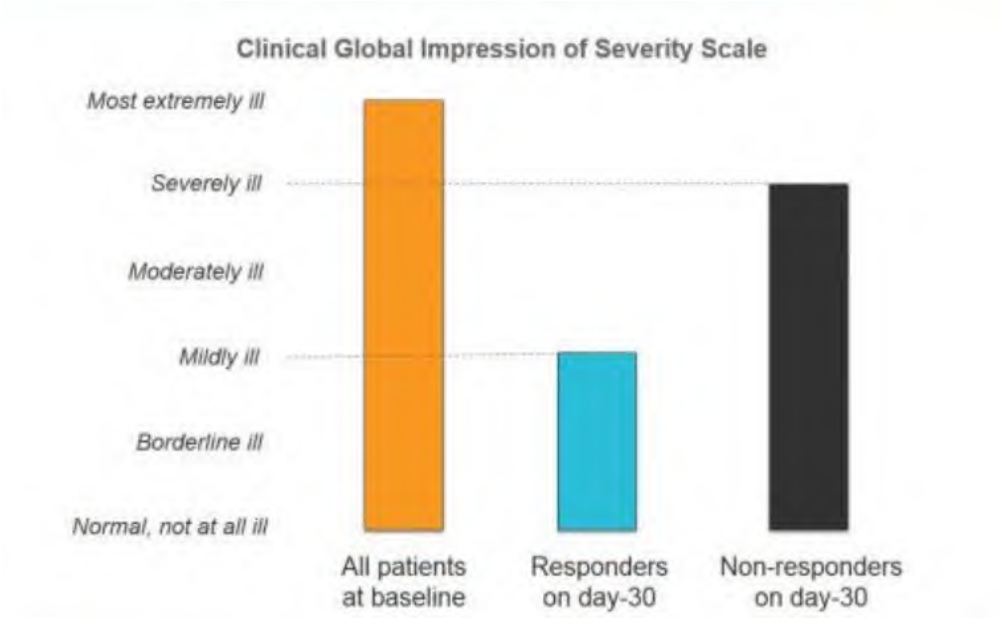
Updated results (Jan 2015) are suggestive of a response rate of 71%. The most recent data update revealed that no drug-related serious adverse events were observed in any of the 20 patients enrolled to date. 17 patients were evaluable for efficacy. In line with initial data, 12 (71%) of these patients were successfully weaned off their anesthetic

agents while on SAGE-547. These 12 patients also remained status epilepticus-free for at least 24 hours after SAGE-547 tapering and were deemed “responders”.

The 8 patients weaned off SAGE-547 and followed for 30 days remained status epilepticus free for this period. Further, these patients were evaluated for improvement in the Clinical Global Impression of Severity (CGI-S) scale, which tracks the severity of brain injury.

- At baseline 19/20 patients were “most extremely ill” and 1/20 was “severely ill”
- Responders to SAGE-547 (patients who were successfully weaned off general anesthesia AND SAGE-547) improved to “mildly ill” (a 3-step improvement) over 30 days
- Non-responders remained “severely ill” after 30 days.

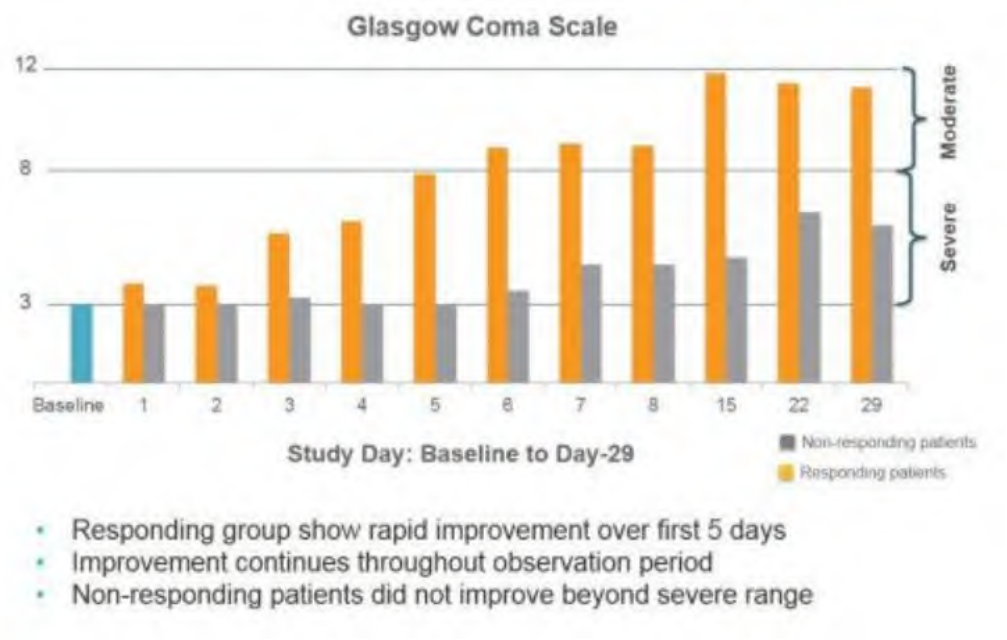
Figure 6: Responders to SAGE-547 Achieved Improvement on the Clinical Global Impression of Severity Scale



Sources: Company reports

Based on the Glasgow Coma Scale (GCS), the responder patients (n=12 of the 17 evaluable) in the Phase I/II achieved rapid improvement in the first five days, from a score of ~3, to a score of ~8. Generally, a score of below 8-9 is associated with severe brain injury. Non-responder patients (n=5 of the 17 evaluable), however, continued to score ~3 on the GCS. After day 5, responding patients continued to improve beyond the severe range (Figure 7), and scored levels as high as 11-12 following day 15. These scores correspond to moderate brain injury. In contrast, non-responder patients did not achieve scores beyond the severe range and remained below 8.

Figure 7: Responders to SAGE-547 Achieved Significant Improvement on the Glasgow Coma Scale



Sources: Company reports

Importantly, the safety of SAGE-547 was encouraging, in light of the different status epilepticus etiologies (n=4, brain hemorrhage; n=4, infections; n=2, worsening of seizures; n=2 primary or metastatic brain tumors; n=1 of each: stroke, sickle cell anemia, lupus, posterior reversible encephalopathy syndrome, and toxic ingestion; n=3, unknown causes).

Emergency IND patients: 78% response rate (7/9 patients) and no drug-related serious AEs

In addition to the Phase I/II ongoing study, SAGE has also evaluated SAGE-547 in an emergency use program, filed with the FDA as an “emergency investigational new drug” (eIND). SAGE announced most recent updates from this program in January 2014. This program consisted of 10 patients of which 6 were males and 4 were females. This program evaluated the proportion of patients who remained SRSE free after weaning both general anesthetic agents as well as SAGE-547. Unlike the Phase I/II study, the

trial did not assess the proportion of patients who were SRSE-free while on SAGE-547 treatment.

In 9 patients treated with SAGE-547 via the eIND mechanism, 78% (7/9) achieved the primary endpoint of no SRSE after weaning form both general anesthetics (GA) and SAGE-547 at 24 hours or later. There were no drug-related SAEs.

These updated results as of Jan 2015 follow on initial promising data, with 5/7 patients having achieved a response (i.e. remained SRSE-free after weaning from both SAGE-547 and general anesthetics).

Individual patient narratives on SAGE-547 from eIND use

Patient #1 was a previously healthy 23 year-old male who developed SRSE with an unknown cause. Anesthetic agents achieved burst suppression, but multiple attempted weans were unsuccessful. After 92 days of SRSE, he was treated with an earlier formulation of SAGE-547 concomitantly with other anti-epileptic drugs including lacosamide, phenobarbital, clonazepam, levetiracetam, bromides, and the ketogenic diet. After initiation of SAGE-547, normalization of EEG was achieved over the next 48-72 hours, and the patient was successfully weaned from general anesthetics and then from SAGE-547. This patient has been discharged and eventually returned home.

Figure 8: 5 out of the First 6 Patients Treated with SAGE-547 via eIND Achieved Resolution of Status Epilepticus

Super-Refractory Status Epilepticus – Emergency-Use Experience

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 >80nM	Yes	Yes	Yes	Yes	No	Yes
Status Epilepticus 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

Sources: Company reports

Patient #2 was a previously healthy 11 year-old female with SRSE likely of autoimmune origin. She received a variety of treatments to achieve burst suppression including

pentobarbital, ketamine, hypothermia, midazolam, and magnesium. Additional drugs used at various times were phenobarbital, valproate, phenytoin, fos-phenytoin, topiramate, lacosamide, and levetiracetam. Immune suppressants were administered to control the underlying autoimmune disorder believed to be the cause of her epilepsy, including methylprednisone, plasmapheresis, intravenous immunoglobulin, rituxan and cyclophosphamide. Upon wean from burst suppression from the above agents, SRSE returned. Immediately prior to SAGE-547 administration, the patient was maintained in burst suppression with the combination of: continuous pentobarbital IV infusion, felbamate, phenytoin, phenobarbital, and ketogenic diet. After two days on SAGE-547, doctors began to taper the pentobarbital infusion. On day five, the patient had been weaned from both pentobarbital and SAGE-547. The patient was free of SRSE, but continued to have brief focal seizures (but not status epilepticus) at a rate of 2-3 seizures per day. This is lower than her previous seizure burden on pentobarbital. One week after the full wean, the patient was awake, responsive to commands, and continued to recover.

Patient #3 was a previously healthy 28 year-old male with depressed mental status with intermittent seizures in the left and right temporal lobes. His EEG progressed to status epilepticus over the following two weeks, but burst suppression was achieved with pentobarbital and ketamine treatment. At the time of administration of SAGE-547, the patient was also being treated with phenytoin, lacosamide, valproate, pregabalin, pyridoxine, magnesium, intravenous immunoglobulin and steroids. The patient developed sepsis just before the start of SAGE-547 dosing, leading to the discontinuation of pentobarbital as SAGE-547 dosing began. EEG activity improved over the 5-day infusion, and continued to improve over the 3 days following discontinuation of study drug. The patient's seizures were considered controlled with a combination of oral anti-seizure medications, and he was subsequently transferred to a step-down unit for further recovery.

Patient #4 was a 2 year-old female with a 2-month history of epilepsy that turned into SE due to an unknown cause. Initial therapy consisted of levetiracetam and phenobarbital, with subsequent treatments including pyridoxine, methylprednisone, benzodiazepines, propofol, and midazolam. Burst suppression was achieved with the combination of midazolam and pentobarbital. At the time of SAGE-547 administration, concomitant medications included pentobarbital, midazolam, phenobarbital, levetiracetam, and dopamine. Midazolam was successfully tapered, and the pentobarbital dose-reduced, within 24 hours of starting SAGE-547. After SAGE-547 taper, the patient was no longer in SE. The patient was found to have significant brain atrophy via MRI, which was believed to be due to her underlying condition, although no definitive diagnosis could be made.

Patient #5 was a previously healthy 17 month old male presenting with complex febrile seizures which progressed to RSE. Increasing doses of midazolam, phenobarbital, levetiracetam, and lorazepam were insufficient to achieve burst suppression. Despite adequate pentobarbital levels via continuous infusion, breakthrough seizures continued. SAGE-547 was administered, but plasma levels above 150 nM were never achieved. A midazolam wean was attempted, but lead to recurrence of seizure and re-titration of midazolam. No drug-related adverse events were reported.

Patient #6 was a 14 year-old female with a history of progressive myoclonic epileptic encephalopathy and a history of RSE that had previously responded to pentobarbital or midazolam. During her most recent bout with SE, she was treated with IV midazolam plus ethosuximide, levetiracetam, clobazam, and the ketogenic diet. The patient had failed multiple attempted midazolam weans. Burst suppression was achieved with the combination of pentobarbital + midazolam, but the initial weans were unsuccessful. One day after completing SAGE-547 administration, the patient was weaned from both midazolam and pentobarbital. Three days after completion of SAGE-547 treatment, the patient was no longer in SRSE. Her EEG is normalizing and she had begun to respond to simple commands.

Patient #7 was a pediatric (age ~8 years old) male, who failed to achieve resolution of SRSE either during the course of or soon after treatment of SAGE-547.

Results to Date Appear Highly Promising Versus <50% Described in the Literature and Cited by Physicians

We view SAGE-547's 73% response rate as promising compared to the 43% and 22% response rates seen with standard of care, propofol and barbiturates, respectively (Rosetti et al., 2011). The response rate is defined as the ability to bring the patient out of a medically induced coma, or to "wean" the patient off standard of care general anesthetics as well as SAGE-547.

Furthermore, the key opinion leaders (KOL) we spoke with note that standard of care yields in the most optimistic ~30-40% response rates in SRSE patients. They view these data as impressive, especially in light of the lack of SRSE reoccurrence within the 24 hour discontinuation window.

Physician Consultants Were Impressed with the SAGE-547 Results to Date

KOL neurologists we spoke with cited the high mortality rates associated with SRSE, of ~40%, and expect that less than a third of patients will return to a no-seizure baseline with weaning of medication.

Physicians believe that the mechanism of action of SAGE-547 is well-suited for the drug's use in SRSE. They note allopregnanolone's ability to modulate both synaptic and extra-synaptic GABA receptor molecules. They also cited preclinical data suggesting that the higher the exposure to currently available GABA-targeted agents, the lower the availability of synaptic GABA receptor. The belief is thus that patients who fail multiple rounds of therapy harbor less available GABA receptor for modulation via benzodiazepines or barbiturates.

KOLs cite the cost to the system for SRSE patients, who can remain in the hospital for months. The current thinking is that for some patients maintained under medication for a long time, SE may resolve itself. KOLs cite a limited understanding of what exactly may cause the disease to resolve itself, leading to seizure cessation. Moreover, SRSE patients that are successfully weaned off from AEDs have already been exposed to a slew of agents, thereby rendering it difficult to discern which one was active.

Our KOL consultants note the difficulty of designing a well-controlled pivotal study. Based on the variability of treatments (choice and sequence of anesthetics) given at different centers or even within a single center, it may be difficult to design or mandate a specific control arm. They believe that a single arm study evaluating a patient's propensity to remain SRSE-free could be appropriate for registration. Historically, there is a narrow band for response rates (% of patients who are successfully weaned off general anesthetics) and survival rates in SRSE patients.

Our consultants believe that a pivotal trial would be very easy to enroll. The typical number of cases per center per year could be almost automatically considered as "enrolled". *"By the time patients reach SRSE there are few legally-authorized representatives that would not agree to have a patient try a new medication".*

Our consultants believe that the SAGE-547 results to date with ~71-78% response rate were "impressive", given the lack of status epilepticus for at least 24 hours post weaning.

An End of Phase II Meeting with the FDA in Q1/15 Should Provide Clarity on a SAGE-547 Registration Trial

SAGE is currently planning a pivotal study for SAGE-547, to begin in mid-2015. The trial design details will be finalized after the company receives input from the FDA, with an End-of-Phase II meeting slated to take place in Q1/15. The company has guided that it will communicate the results from the EOP2 meeting in Q1 2015. The efficacy endpoint of the pivotal trial will likely be the proportion of patients to remain SRSE-free for 48 hours after general anesthetic tapering while on SAGE-547, and at least 24 hours after tapering off SAGE-547. Further, patients will be followed for at least 14 days. With respect to the patient populations and times to enrollment, we spoke with management, who outlined two most likely scenarios, to entail 100-200 patients for 1-2 years.

The first potential scenario entails a two-arm, controlled trial. Management noted that in the Phase I/II study and the eIND program, SAGE-547 was administered in addition to standard-of-care. Moreover, physicians were not limited in their choice of what this standard-of-care could be, and responses to date were achieved with variable drug combinations. Should patients in the control arm fail to wean off general anesthetics, they would have the option to cross over to the SAGE-547 arm. We believe that this study would likely require ~200 patients. Given that investigators can currently determine very rapidly if patients do not respond to SAGE-547 treatment, we believe a controlled-trial

could be completed ahead of the higher end of the company's guidance of ~1-2 years. In the more conservative scenario pivotal data could become available ~2 years after the anticipated mid-2015 start, in mid-2017.

A single-arm pivotal study may allow for a smaller trial size, more rapid readout. Based on the 70%+ response rates seen to date with SAGE-547, SAGE believes institutional review boards (IRBs) at potential trial sites may oppose the use of a control, standard of care arm. In this scenario, a single arm trial could support registration, with efficacy rates to be compared with historical responses. Such a study could require ~100 patients and its duration would likely be at the lower end of the company's 1-2 year time-to-completion guidance. In this scenario, pivotal data for SAGE-547 could be available within 1 year from the mid-2015 expected study start, in mid-2016.

We forecast $1.7B in peak SAGE-547 WW sales in 2026

Based on our review of the literature, we estimate there are ~140K status epilepticus patients diagnosed in the U.S. per year (we blend the published prevalence of 41 per 100,000 per Trinka et al. 2012 and SAGE's 150K estimate based on market research). Additionally, we estimate that ~22.6% of status epilepticus episodes become refractory SE after failure of first- and second-line antiepileptic treatments (Novy et al. 2010), resulting in ~32K refractory SE patients in the U.S. per year. We believe over 50% of those refractory status epilepticus patients will likely become super refractory, likely as high as ~70% (Shorvon and Ferlisi, 2011), resulting in ~22K super-refractory status epilepticus (SRSE) patients per year. This estimate in in line with SAGE's estimate of ~25K SRSE patients in the U.S. per year.

Our projected revenue comes solely from lead asset SAGE-547. We estimate that 140K patients develop SE per year in the U.S., 206K in the broad E.U., and 206K in the addressable rest-of-the-world countries, with 22K, 35K, and 35K progressing to SRSE, respectively. We conservatively assume positive data from the pivotal trial mid-2017 (the higher end of the 1-2 years management guidance and pivotal trial start mid-2015), leading to approval and commercialization in mid-2018 in the U.S., mid-2019 in the E.U., and late-2019 in ROW. We assume that SAGE goes it alone for commercialization in the E.U., given management commentary suggesting they are not actively looking for a partnership – which we believe is the correct approach given the orphan nature of this indication (small patient numbers; known treatment location of patients). We note the high cost associated with hospital stays for SRSE patients, with a median survival rate of 11 days associated with a ~140K cost (per SAGE analyses). Management guided that pricing for a round of SAGE-547 treatment could range between $25K and $75K. We conservatively assume $50K/patient, but note that therapies such as BMRN's Kuvan that address ~25-30K patients are priced at ~$100K per year and SAGE-547 is a fixed-duration therapy with a potentially transformative clinical benefit. We conservatively assume a 20% gross-to-net discount for hospital-negotiated rates. We model for peak penetration of 72% in the U.S. (slight uptick from 70% in 2025 when Orphan Drug

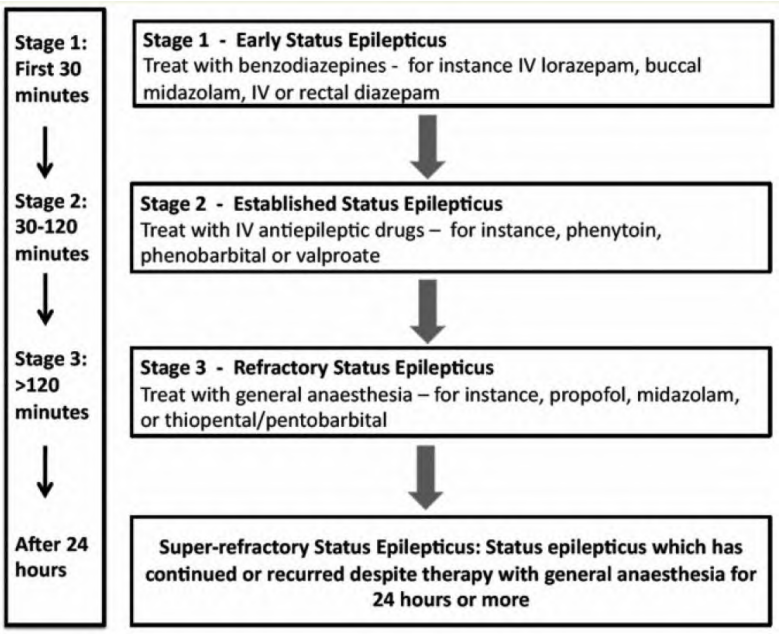
exclusivity ends), 40% in the E.U., and 9% in ROW in 2026. We forecast peak SAGE-547 revenue of $955M in the U.S. in 2026 based on SRSE sales alone (we conservatively do not assume any off-label use of SAGE-547 in earlier lines of status epilepticus therapy); peak E.U. sales of $590M in 2026 and peak ROW sales of $134M. We also do not currently model for sales from proof of concept indications ET and PPD, as well as other pipeline assets, and note that they provide upside to our model.

The Current Status Epilepticus (SE) Treatment Algorithm Comprises 4 Distinct Steps

1. Patients diagnosed with early SE experience a seizure lasting longer than 5 minutes (Figure 9).
2. Patients failing benzodiazepines as first line therapy progress to established SE, which is typically at 30-120 minutes into the seizure, where they are treated with increasingly powerful drugs including barbiturates (ex. phenobarbital, pentobarbital) and 2nd line anti-epileptic drugs (AEDs). These are typically phenytoin, valproate, levetiracetam, and several others, with a variety of mechanisms of action including sodium channel blockade, calcium channel blockade, HDAC inhibition, increasing GABA levels in the brain, and AMPA/kainite channel blockade.
3. Once SE has progressed past 120 minutes, the patient has likely failed to break the seizure, and a general anesthetic (usually propofol, possibly with the addition of a benzodiazepine and/or a barbiturate) should be administered to prevent ongoing brain damage.
4. If the patient is either unable to achieve EEG normalization or fails an attempted wean (goes back into SRSE upon wean), they are considered to be in super refractory status epileptics (SRSE).

Not only there are no currently approved therapies for SRSE, but there have never been any completed randomized studies in the condition. The general strategy is to attempt the use of multiple treatments with different mechanisms of action (general anesthetic + barbiturate + benzodiazepines + other 2nd line AEDs + other treatments such as hypothermia) to achieve EEG normalization, and then try to wean the patient based on the physician's judgment.

Figure 9: The SE/RSE/SRSE Treatment Paradigm

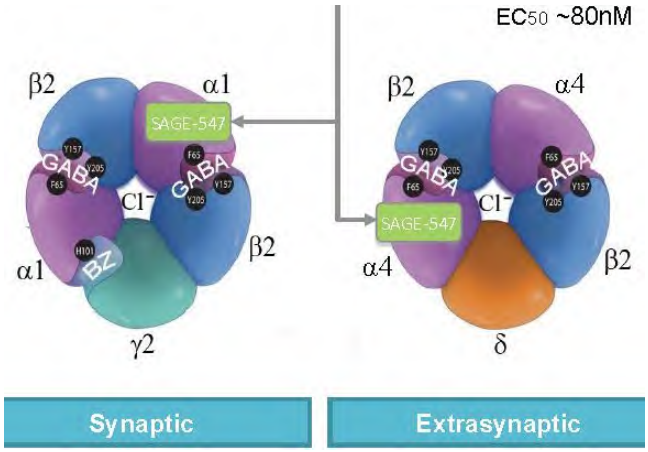


Sources: Shorvon and Ferlisi, 2011, Brain.

First-line patients are typically treated with benzodiazepines (BDZs), with midazolam being one the strongest and most widely used in SE.

Benzodiazepines bind to the α1 subunits GABA-A receptor, which is typically expressed at the synapse of one neuron on to another (Figure 10). While this allows benzodiazepines to achieve phasic inhibition of neuronal signaling, it is insufficient to control many types of status epilepticus. Patients who stay in status epilepticus upon administration of benzodiazepines are then classified as 2nd line status epilepticus patients with established status epilepticus (Figure 9).

Figure 10: Two GABA-A Channel Subtypes and Drug-binding Locations



Sources: Shorvon and Ferlisi, 2011, Brain.

Benzodiazepines do not bind, and thus do not modulate the α4-containing (mostly α4β2δ and α4β3δ) GABA receptors, which are predominantly expressed outside the synapse (extrasynaptic locations). Modulation of the α4-containing GABA receptors allows for tonic inhibition, which in many cases leads to burst suppression (aka normalization of EEG for a patient in status epilepticus). SAGE-547 is potent at both the α1- and α4-containing GABA-A receptors, which provides an opportunity for the novel drug to have increased efficacy over benzodiazepines.

Second-line patients typically receive combinations of barbiturates and other AEDs.

Drugs used in the second line setting typically include barbiturates (phenobarbital) and other AEDs with more diverse mechanisms of action including phenytoin, levetiracetam, and valproate. These drugs are able to achieve burst suppression in ~30% of second line patients, leaving 70%, or ~30K RSE patients in the U.S. in need of third-line therapy. Physicians will typically know if a patient is refractory SE within 30-120 minutes of the first treatment upon hospital admission.

Third-line (RSE) patients are treated with general anesthesia to induce coma

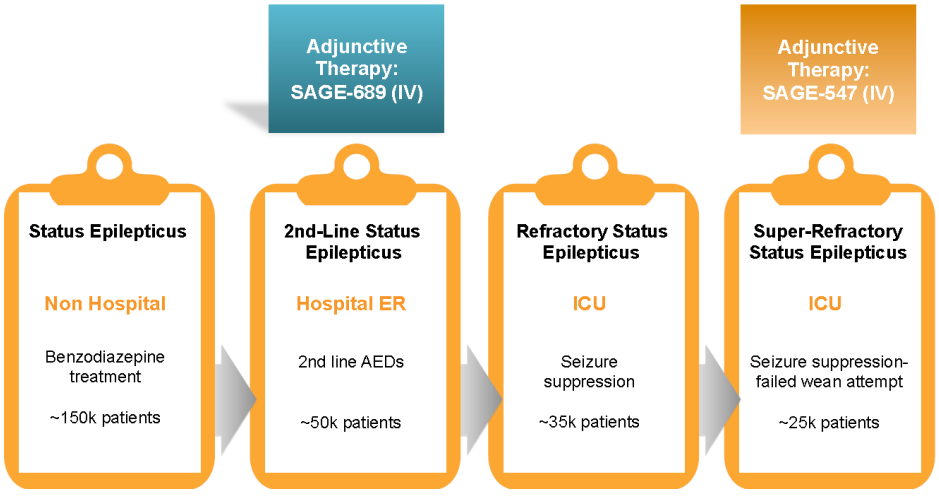
If a patient has not achieved EEG normalization within ~120 minutes of treatment with first and second line AEDs, a medical coma should be induced to attempt to minimize any further neurological damage. Although remaining in a state of coma for longer periods of time can lead to physical atrophy and muscle wasting, the neurological side effects are usually minimal as long as EEG is normalized and seizure activity is halted. RSE patients becomes super refractory (SRSE) when wither they failed to achieve EEG normalization or when SE recurs after wean from the general anesthetic. At that point, there is very little published evidence or guidelines of how to handle these patients. Most neurologists continue to treat with combinations of multiple anesthetics, anti-epileptic agents, and even other treatments such as hypothermia (cooling the patient down) and

ketogenic diet. There is both a high unmet need for novel therapies in this setting, in addition to a need for better data from well-controlled trials to differentiate between the current treatment options that physicians have at their disposal.

SAGE-547 and SAGE-689 may cover a wide spectrum of the SE treatment paradigm

While SAGE's lead drug, SAGE-547 will be developed for SRSE, a condition in which patients have no satisfactory alternatives, SAGE is also planning to enter other segments of the SE continuum from 2nd line to later (Figure 10). SAGE-689 is slated to begin development for 2nd line SE in situations where a shorter hospital stay and more easily tunable PK may be desirable. SAGE could have a dominant SE franchise that will likely benefit from strong synergies in terms of commercial and R&D spend and market and scientific expertise.

Figure 11: SAGE-547 and 689 Could Address a Broader Spectrum of SE than Solely SRSE Patients



Sources: Company reports

SAGE-547 is Tested as "Probe Molecule" for Essential Tremor

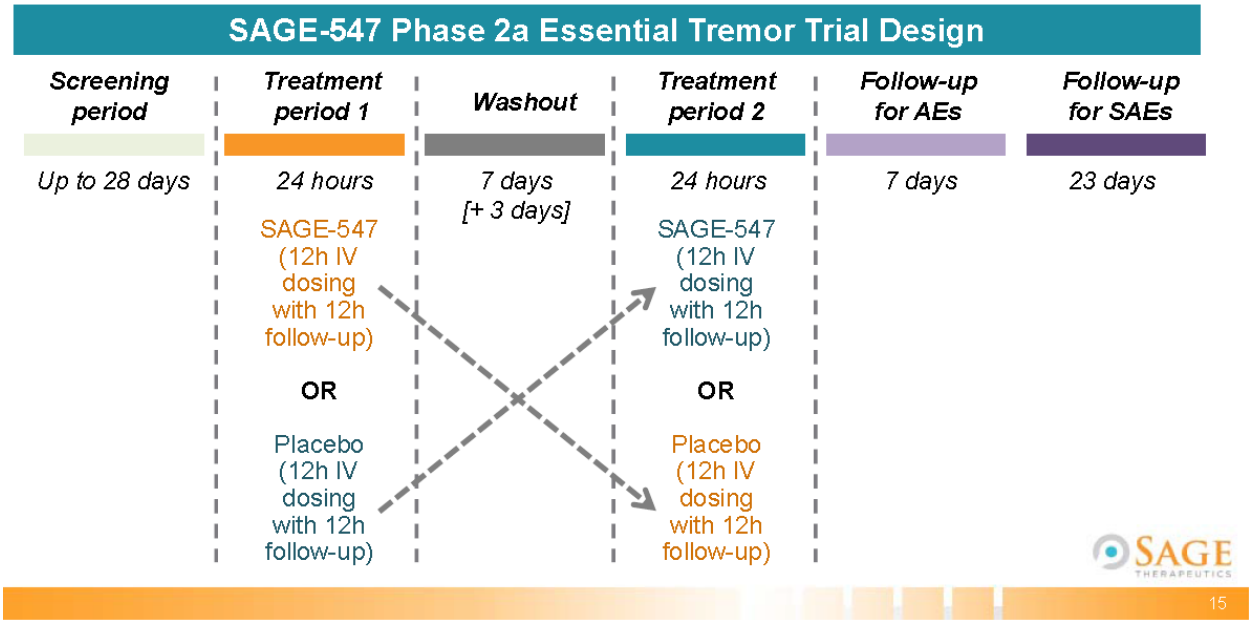
GABA receptor modulation could provide rationale for addressing essential tremor (ET), given that benzodiazepines are currently used to manage ET patients with anxiety. SAGE-547 activity in ET could provide important proof-of-concept data for the development of a novel GABA-targeted molecule in this indication. While benzodiazepines achieve tonic inhibition through potentiation of α1-containing synaptic GABA receptors, SAGE-547 can achieve both phasic and tonic inhibition by potentiating both α1- and α4-containing receptors, possibly leading to greater efficacy in reducing the involuntary movements associated with ET.

ET is a progressive movement disorder caused by abnormal neuronal signaling. ET is the most common movement disorder estimated at 4% of the population above the

age of 40 (Benito-Leon et al. 2006). ET is often misdiagnosed as Parkinson's disease, which is more well-known. Patients are typically older adults, and experience tremors (involuntary movements) in the hands, arms, and head. Tremors may also affect a patient's voice, and get worse when under stress, tired, or when stimulants are used such as caffeine. The cause is thought to be abnormal electrical signals, which shares some similarity with seizure, although not nearly as severe. This provides a nice rationale for the utility of a GABA-targeted molecule informed by potential SAGE-547 activity in the disorder. ET is currently managed with a combination of drugs and other therapies. Other drugs include beta adrenergic blockers (propranolol), anti-seizure drugs (primidone), benzodiazepines (clonazepam, diazepam), and in some cases, botox injections. Other therapies used include surgical lesioning of specific brain regions that may be known to be the causal area of the tremor, and more commonly deep brain stimulation (DBS), which stimulates the brain a high frequency to normalize firing in certain areas. We estimate the prevalence of ET that might require treatment at 23.7 per 100,000 people (Rajput et al 1984), which equates to ~75K patients in the U.S. Given that SAGE intends to use this compound as a "probe" molecules for the development of follow on GABA-targeting compounds in ET, we do not currently include any revenue contribution to this indication.

A Phase II trial of SAGE-547 in ET is ongoing, with data expected in mid-2015. A Phase II study was initiated in September 2014. The trial is a double-blind, placebo-controlled, proof of concept crossover study expected to enroll 24 patients between the ages of 35-75 who have been diagnosed with ET and with symptoms present in at least one arm for at least 2 years prior to screening. This will allow for the key efficacy endpoint of measurement of tremor amplitude by an accelerometer, in addition to each patient's response on the Essential Tremor Rating Scale (TETRAS). SAGE will collect efficacy data over 24 hours for each patient on both the placebo and on drug (each patient serves as their own control).

Figure 12: Phase II Crossover Trial Design for SAGE-547 in Essential Tremor Could Provide Important Proof of Principle



Sources: Company reports

Human and animal data support SAGE-547's chances in severe post-partum depression

Strong evidence for the role of allopregnanolone in post-partum depression (PPD) comes from studies in humans (Nappi et al, 2001) showing statistically significant inverse correlations between blood levels of the hormone and scores on the Hamilton Rating Scale for Depression (lower allopregnanolone and PPD appear correlated per some literature reports). Additional studies in rodents (Evans et al. 2012) have shown that treatment with allopregnanolone can alleviate depression in some models of chronic stress.

PPD is a form of depression affecting some women after childbirth. The symptoms of PPD are consistent with those of depression: sadness, lethargy, changes in eating and sleeping behavior, anxiety, and irritability, among others. Although the precise causes are not well understood, the abrupt hormonal changes corresponding with the birth of a child have been strongly implicated. Treatment can consist of drugs typically used in depression such as selective serotonin reuptake inhibitors (SSRIs), although evidence for those drugs in this indication is not well proven. Other treatments involve counseling and behavioral therapy. In some cases, PPD can be quite severe with high unmet need. An estimated 9-16% of postpartum women will experience PPD. With ~4.0M babies born in the U.S. per year, that equates to ~400K women experiencing symptoms of PPD. We do not currently model for sales of SAGE-547 in PPD, and note that it may provide upside to our estimates.

Initial Phase II data for SAGE-547 in PPD are expected mid-2015. SAGE began an initial open-label proof on concept study on SAGE-547 in severe PPD in early 2015 (trial listed since September 2014). The trial is expected to enroll 10 patients, all female between the ages 18-45. The key efficacy endpoint will be the effects over 4 days on 2 clinical scores for depression: the Hamilton Rating Scale for Depression-17 (HAM-D-17), and the individual Clinical Global Impression-Improvement (CGI-I) Scale. Topline results are anticipated by mid-2015

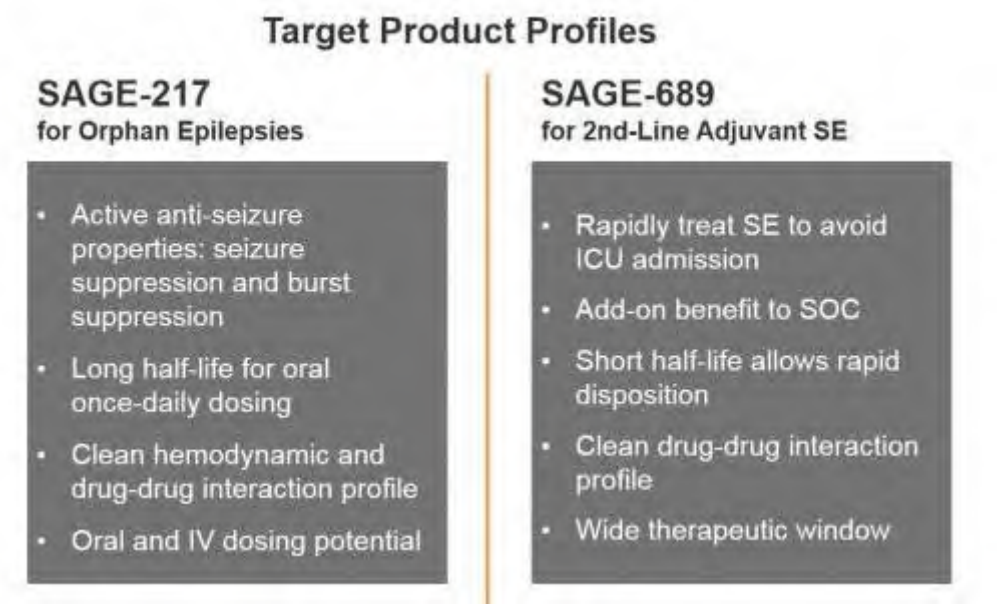
SAGE Noted that SAGE-547 is Being Used as a "Probe" for ET and PPD

The compound would likely not be developed for either of the two indications. However, a signal of activity in these trial could enable the company to select one of the >1500 GABA-modulating molecules to advance into the clinic. Early data from PPD and ET could enable the company to identify compounds with the appropriate oral dosing, PK and PD parameters, and correct biomodulation of the GABA target.

SAGE's Platform of Ion Channel Modulators Provides Multiple Shots on Goal

SAGE is leveraging its expertise in medicinal chemistry to develop robust IP around the GABA modulator space. Beyond lead drug SAGE-547, SAGE is developing two novel compounds: SAGE-689 and SAGE-217, each with PK properties specifically tuned to the way physicians could use them in patients. SAGE-689's short half-life is likely to enable rapid on/off kinetics that will be useful in the outpatient SE setting. SAGE-217 has much longer half-life that could enable once daily, oral dosing for other epileptic indications.

Figure 13: SAGE-689 and SAGE-217 Have Unique Properties Rendering Them Suitable for Different Applications

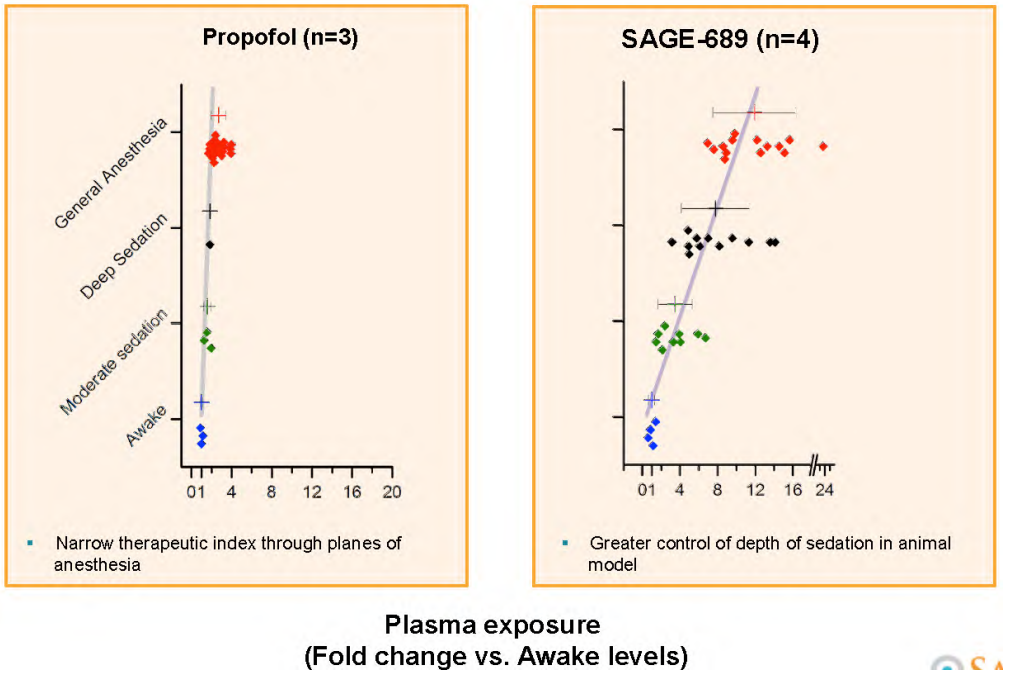


Sources: Company reports

SAGE-689's Short Half-life May Allow Dosing for 2nd Line SE

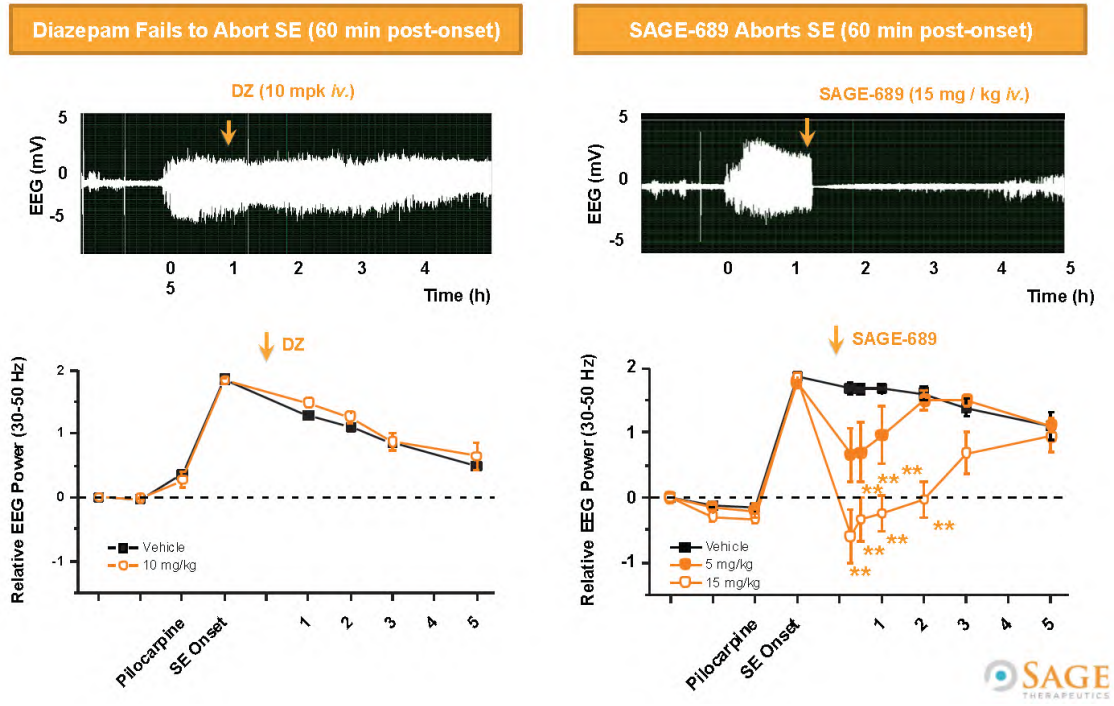
SAGE is developing SAGE-689 for use in 2nd line status epilepticus (SE), which could spare the need for the patient to go into an intensive care unit (ICU). The drug has two major advantages: 1) a short half-life which enables rapid control over plasma drug levels to allow for rapid step-down and discharge from the hospital, and 2) a wide therapeutic window, giving the physician greater control over the degree of sedation compared to propofol, the current standard of care used to induce general anesthesia and burst suppression in SE patients (Figure 14). SAGE-689 demonstrated robust efficacy in the pilocarpine-induced seizure model of epilepsy in rodents (Figure 15). This model is pharmacoresistant to benzodiazepines (diazepam used here), providing some support for the superiority of SAGE-689, with the caveat that induced animal models of epilepsy may not translate perfectly to humans.

Figure 14: SAGE-689 Demonstrates Superior Therapeutic Window for Sedation Level in an Animal Model.



Source: Company reports

Figure 15: SAGE-689 Demonstrates Dose-dependent Termination of Diazepam-resistant SE in Pilocarpine-Induced Seizure Animal Model



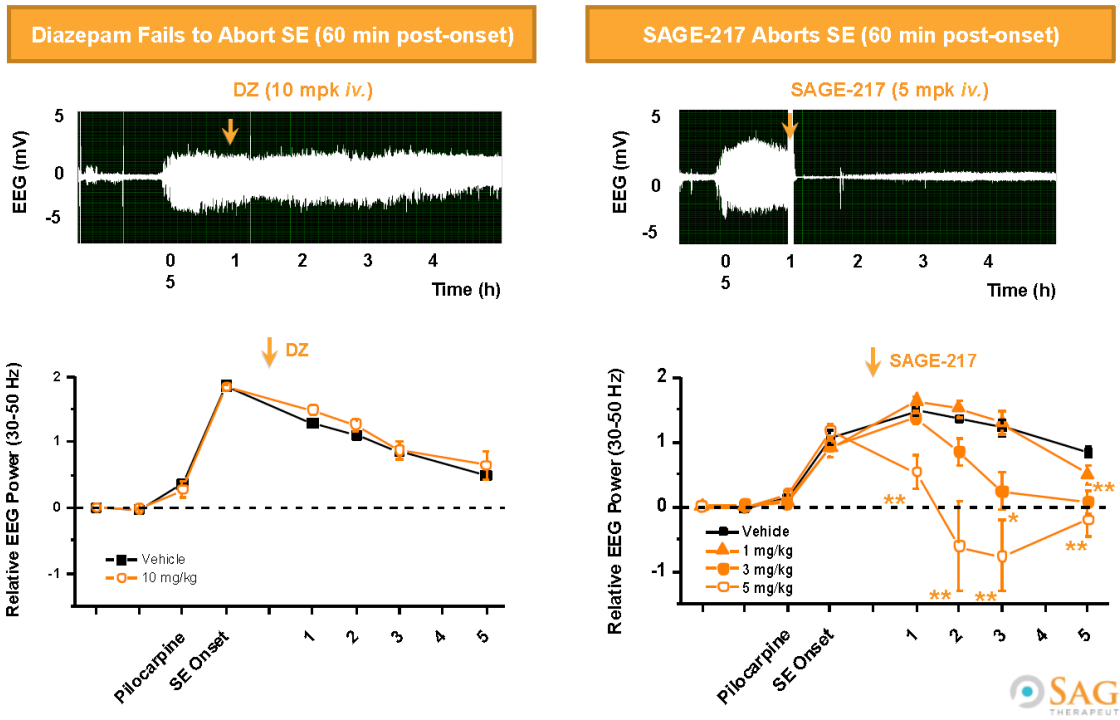
Source: Company reports

SAGE plans to begin Phase I testing of SAGE-689 in late-2015. After completion of the IND filing, SAGE plans to initiate a Phase I trial focusing on safety, pharmacokinetics (PK), and pharmaco-EEG (effect of the drug on electroencephalography) as an initial efficacy measure, and the dose required for sedation/anesthesia and burst suppression (inducing low/no electrical activity in the brain). The design will consist of a Phase Ia portion where 60 minute IV infusions of drug will be evaluated for safety and PK. Doses included in this first portion will be escalated until patients achieve a level of neuronal inhibition consistent with general anesthesia. SAGE will discuss these safety results with the FDA before proceeding to the Phase Ib portion where SAGE-689 will be dose-escalated to achieve burst suppression, providing an initial early measure of efficacy for SE.

SAGE-217's long half-life promises convenience: once-daily oral dosing and 'auto-tapering'

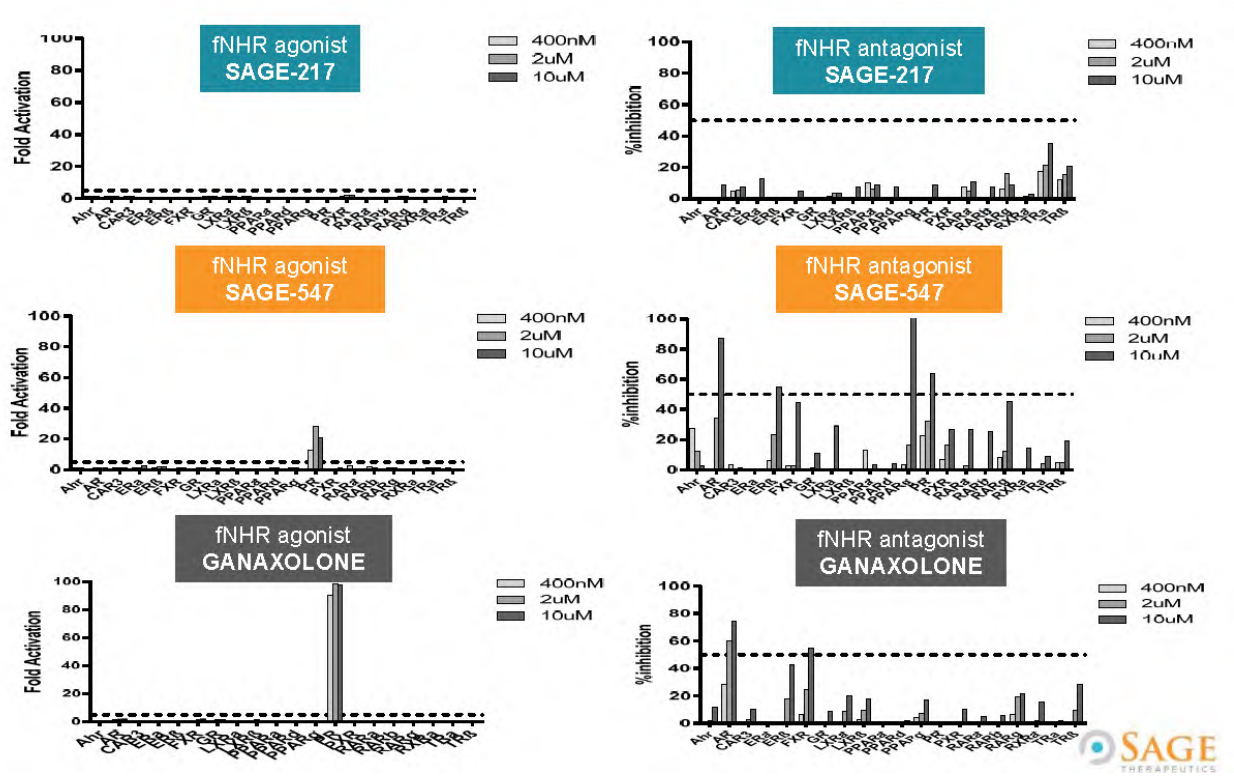
SAGE-217 is another GABA positive modulator that could be formulated both for oral and intravenous use. SAGE has tuned the half-life of this molecule to be much longer to enable once daily dosing, minimize fluctuations of the drug in the blood, and to provide a slow taper of the drug when a patient discontinues therapy. In preclinical studies, SAGE-217 has demonstrated efficacy in rodent models of epilepsy that are refractory to the benzodiazepine diazepam (Figure 16); the same model was used to test SAGE-689, above. Combined with the similarity of SAGE-217 to SAGE-547 in terms of the mechanism of inhibition of specific GABA subtypes, SAGE-217 could be substantially de-risked if SAGE-547 demonstrates efficacy in its pivotal trial. In terms of safety, SAGE-217 appears to have minimal off-target effects (Figure 17), which may confer a safety profile amenable to long term, chronic use. SAGE plans to begin Phase I in another undisclosed orphan genetic disorder by Year-End 2015.

Figure 16: SAGE-217 Demonstrates Dose-dependent Termination of Diazepam-resistant SE in Pilocarpine-Induced Seizure Animal Model



Source: Company reports

Figure 17: SAGE-217 Demonstrates Minimal Off-Target Effects, Which Likely Confers a Safety Profile Acceptable for Chronic Use.



Source: Company reports

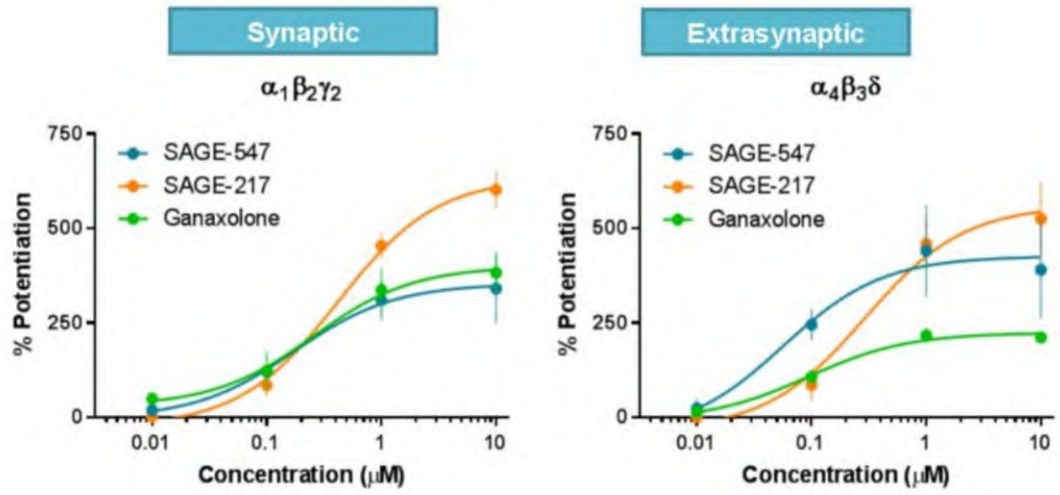
Competition is Limited in Status Epilepticus

We view competition as limited for SAGE as SRSE is a neglected disease with few therapies in development. Marinus Pharmaceuticals, GW Pharma, and H. Lundbeck are developing drugs for other forms of epilepsies. All three drugs are formulated orally, which makes them inappropriate for use in unconscious SRSE patients. Either drug could potentially compete with SAGE's future products in orphan genetic CNS disorders.

Marinus is developing ganaxolone, but unlikely to compete directly with SAGE

Although ganaxolone shares a similar mechanism of action (GABA-A positive modulator) to SAGE-547, it is unlikely to threaten SAGE-547 or any follow-on compounds in SE as it is 1) not currently in development for any form of SE, 2) is only formulated for oral dosing, thus precluding use in unconscious SRSE patients. Additionally, ganaxolone is less efficacious on α4-containing GABA-A receptors (extrasynaptic) (Figure 18), which is the primary differentiation of SAGE-547 compared to currently marketed products.

Figure 18: Ganaxolone is Less Efficacious than SAGE-547 on Alpha-4 Containing GABA-A Receptors Which are a Key Point of Differentiation



Source: Company reports

GW Pharma is developing epidiolex for pediatric epilepsies, including Dravet syndrome and Lennox-Gestaut Syndrome (LGS). Epidiolex is a formulation of plant-derived canabidiol for pediatric epilepsies. While we do not believe epidiolex will compete with SAGE-547 in SRSE as it is formulated orally (not appropriate for unconscious patients), it may compete with SAGE's potential future products in orphan diseases such as Dravet syndrome. Epidiolex has a different mechanism of action from any of SAGE's proposed drugs, and therefore could possibly be complimentary.

H. Lundbeck's Onfi is approved for the Lennox-Gastaut Syndrome, about to begin Phase III testing for Dravet syndrome. Onfi or clozabam is a benzodiazepine that functions through a similar mechanism to generic benzodiazepines. The product is approved in Europe but its efficacy in SRSE is presumably comparable to other standard of care benzodiazepines commonly used in the U.S.

Intellectual Property

SAGE classifies its patent portfolio into 3 main categories: SAGE-547, novel GABA-A receptor modulators, and novel NMDA receptor modulators. For SAGE-547, SAGE owns two patent families. The first is directed towards compositions combining allopregnanolone (the main active ingredient) and cyclodextrins (which improve the PK of allopregnanolone). If issued, this family would expire in January 2033. The second family is directed towards method of use of allopregnanolone to treat seizure disorders such as status epilepticus, and various dosages and schedules of treatment. The initial IP in this family would expire in August 2023, if issued.

For its novel GABA-A receptor modulators, SAGE has exclusively licensed a portfolio of IP applications from Washington University directed towards both composition of matter and methods of use for compounds targeting these receptors. Additionally, SAGE has a jointly owned patent application covering SAGE-689 that would expire in December, 2033. SAGE is the sole owner of a patent application directed towards composition of SAGE-217, which would expire in October 2022 or later.

For the NMDA program, SAGE owns three families of patent applications directed towards NMDA modulators. Two cover composition of matter for novel compounds, while the third covers a biomarker that could be used to select patients who might benefit from an NMDA modulator compound. If issued, patents form these families would expire between September 2032 and March 2034.

Financials

As of September 30, 2014, SAGE had cash, cash equivalents, and marketable securities of $136.7M. GAAP operating expenses for were $9.47M, and $21.5M for the three and nine months ended September 30, 2014. As of November 1, 2014, the company had ~25.8M shares outstanding and ~1.78M common stock equivalents (options to purchase common stock and restricted stock).

We do not project any revenue for SAGE until 2018, at which time we assume SAGE-547 approval (conservatively model for a 2-year trial at the high end of management guidance of 1-2 years) for SRSE in the U.S. and forecast revenue of $63.8M, $332.8M, and $545.5M for 2018, 2019, and 2010, respectively.

We model for a continuing ramp-up in quarterly expense in 2015 and 2016, as the pivotal trial of SAGE-547 begins in mid-2015 and novel products move into the clinic in late-2015 and 2016. We forecast that the company will achieve profitability in 2019.

The company raised $94M with its initial public offering in July 2014, and shares are up 118% over the S1 price based on the 01/23/15 closing price. We believe SAGE has a cash runway into 2016, and we model for two follow-on equity offerings to support continuing activities: 1) an equity offering of ~2.857M shares at $70/share in early 2016, and 2) an equity offering of ~1.66M shares at $120/share in mid-2017, after a potential data readout from the SAGE-547 pivotal study.

Management and Compensation

SAGE is led by an experienced management team with deep experience across multiple functions across chemistry, biology, clinical development, and commercialization.

Jeff Jonas, Chief Executive Officer

Dr. Jonas boasts more than 20 years of experience in the CNS field, on both the scientific and business sides of the pharmaceutical and healthcare industries, as President of the Regenerative Medicine Division and Senior Vice President of Research and Development at Shire, executive Vice President of ISIS Pharmaceuticals, as the Chief Medical Officer and Executive Vice President of Forest Laboratories, Inc. Dr. Jonas also founded several other healthcare companies. Dr. Jonas received his B.A. from Amherst College and M.D. from Harvard Medical School. He completed a residency in psychiatry at Harvard and then served as Chief Resident in psychopharmacology at McLean Hospital, Harvard Medical School.

Kimi Iguchi, Chief Financial Officer

Ms. Igichi has extensive experience in the financial and operating areas through her senior management previous at Millennium, Biogen and emerging life science companies. She also served as the Chief Operating Officer, North America, for Santhera Pharmaceuticals and held the role of Vice President of Finance at Cyberkinetics Neurotechnology Systems. Previously, Kimi was the Senior Director of Financial Reporting and Analysis at Millennium Pharmaceuticals and the Senior Manager of External Reporting at Biogen, Inc. She also worked as a business assurance manager at PricewaterhouseCoopers LLP and started her career in chemistry-related positions at various Boston-based companies. Ms. Iguchi holds a B.A. in chemistry from Drew University and an MBA from Northeastern University and a CPA.

Steve Kanes, Chief Medical Officer

Dr. Kanes is trained in psychiatry and has extensive experience in the CNS space through his tenure as Executive Director/Therapeutic Area Clinical Director of the inflammation, neuroscience and respiratory division of AstraZeneca Pharmaceuticals. He remains a faculty member in the psychiatry department at the University of Pennsylvania School of Medicine. Dr. Kanes has authored or co-authored more than 30 peer-reviewed publications and serves as an ad hoc reviewer for the journals Neuropsychopharmacology, American Journal of Medical Genetics and Biological Psychiatry. Dr. Kanes received his B.A. from the University of Pennsylvania and both his Ph.D. and M.D. from State University of New York, Stony Brook. He completed his psychiatry residency at Yale-New Haven Medical Center and postdoctoral fellowship at the University of Pennsylvania.

Tom Anderson, Chief Commercial Strategy Officer

Mr. Anderson served in various high-responsibility positions at Shire, and has extensive experience in the CNS space (specialty pharmaceutical commercial operations, business information and strategic marketing functions, business development experience). He also served in senior level positions at Johnson & Johnson's pharmaceutical companies, (Janssen and Ortho-McNeil), involved with marketing, marketing research, sales and sales management, operations and engineering. He also served as President and Chief Executive Officer of a dental products company called Ranir Corporation, where he was also a Corporate Officer and Director, and Executive Vice President and Chief Operating Officer of Lander Co., Inc., a healthcare-related consumer packaged goods company, where he was previously a Corporate Officer.

Al Robichaud, Chief Scientific Officer

Dr. Robichaud has more than 20 years of drug discovery in the CNS field. He served as Vice President of Chemistry and Pharmacokinetic Sciences at Lundbeck USA (experience in drug discovery, analytical, computational and pharmacokinetics focused on synaptic transmission and neuroinflammation). Dr. Robichaud has served as Senior Director and Head of the Neuroscience Discovery Chemistry Department of Wyeth

Research (leading a group that delivered more than 15 CNS drug candidates into clinical development). Al has co-authored more than 125 manuscripts and abstracts, and is a co-inventor on 50 patents and patent applications. Dr. Robichaud holds a B.S. in chemistry from Rensselaer Polytechnic Institute, a Ph.D. in organic chemistry from the University of California, Irvine and was an American Chemical Society postdoctoral fellow at Colorado State University.

In our view, SAGE management's incentives are well-aligned with shareholders. Compensation is a mix of base salary, annual cash bonus, and long-term incentive awards that include stock options (Figure 19). We expect the compensation committee will issue more options and restricted stock awards to management in the future.

Figure 19: SAGE Executives' Pay is Balanced Between Salary and Options

Executive Officer	Position	Base Salary ($)	Bonus ($)	Option Awards ($)	Other ($)	Total ($)
Jeffrey M. Jonas, M.D.	Chief Executive Officer	152,973	—	204,774	228,000	585,747
Stephen J. Kanes, M.D., Ph.D.	Chief Medical Officer	148,958	—	65,150	65,000	279,108
Albert J. Robichaud, Ph.D.	Chief Scientific Officer	300,000	2,500	—	—	302,500

Source: Company reports

Sage Therapeutics

(NASDAQ: SAGE)

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Consolidated Income Statement

($thousands, except per share data)	FY 2012A	FY 2013A	Mar Q1 2014A	Jun Q2 2014A	Sep Q3 2014A	Dec Q4 2014E	FY 2014E	FY 2015E	FY 2016E	FY 2017E	FY 2018E	FY 2019E	FY 2020E	FY 2021E	FY 2022E	FY 2023E	FY 2024E	FY 2025E	FY 2026E
Revenue																			
SAGE-547	$ -	$ -	-	-	-	-	$ -	$ -	$ -	$ -	$ 63,810	$ 332,738	$ 545,591	$ 809,859	$ 951,793	$ 1,130,111	$ 1,394,818	$ 1,564,672	$ 1,680,410
Total Revenue	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 63,810	$ 332,738	$ 545,591	$ 809,859	$ 951,793	$ 1,130,111	$ 1,394,818	$ 1,564,672	$ 1,680,410
COGS	-	-	-	-	-	-	-	-	-	-	5,105	36,601	60,015	89,084	95,179	113,011	139,482	156,467	168,041
Gross profit	-	-	-	-	-	-	-	-	-	-	58,705	296,137	485,576	720,774	856,614	1,017,100	1,255,336	1,408,205	1,512,369
Operating expense																			
R&D (GAAP)	7,229	14,357	4,173	4,381	6,601	8,005	23,160	45,302	60,221	70,224	80,334	90,211	100,260	110,299	120,317	130,877	140,903	150,756	160,901
SG&A (GAAP)	2,402	3,922	1,617	1,807	2,869	3,215	9,508	14,343	23,556	48,910	74,002	79,043	84,056	89,054	94,829	99,901	104,055	109,007	114,018
Stock-based compensation	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Total operating expense	9,631	18,279	5,790	6,188	9,470	11,220	32,668	59,645	83,777	119,134	154,336	169,254	184,316	199,353	215,146	230,778	244,958	259,763	274,919
Operating income (loss)	**(9,631)**	**(18,279)**	**(5,790)**	**(6,188)**	**(9,470)**	**(11,220)**	**(32,668)**	**(59,645)**	**(83,777)**	**(119,134)**	**(95,631)**	**126,883**	**301,260**	**521,421**	**641,468**	**786,322**	**1,010,378**	**1,148,442**	**1,237,450**
Interest Income (expense), net	-	1	-	1	3	4	8	20	35	55	59	92	214	428	748	1,205	1,830	2,560	3,406
Other income (expense), net	(1)	(3)	-	(5)	(1)		(6)	-	-	-	-	-	-	-	-	-	-	-	-
Total Other Income	(1)	(2)	-	(4)	2	4	2	20	35	55	59	92	214	428	748	1,205	1,830	2,560	3,406
Income before income taxes	(9,632)	(18,281)	(5,790)	(6,192)	(9,468)	(11,216)	(32,666)	(59,625)	(83,742)	(119,079)	(95,571)	126,975	301,474	521,849	642,216	787,527	1,012,208	1,151,002	1,240,856
Provision for income taxes	-	-	-	-	-	-	-	-	-	-	-	12,698	30,147	78,277	192,665	236,258	303,662	345,301	372,257
Net gain (loss)	**(9,632)**	**(18,281)**	**(5,790)**	**(6,192)**	**(9,468)**	**(11,216)**	**(32,666)**	**(59,625)**	**(83,742)**	**(119,079)**	**(95,571)**	**114,278**	**271,327**	**443,572**	**449,551**	**551,269**	**708,545**	**805,702**	**868,599**
Accretion of redeemable convertible preferred stock	(4)	(7)	(326)	(1,577)	(391)	(391)													
Net gain (loss) applicable to common shareholders	$ (9,636)	$ (18,288)	$ (6,116)	$ (7,769)	$ (9,859)	$ (11,607)	$ (32,666)	$ (59,625)	$ (83,742)	$ (119,079)	$ (95,571)	$ 114,278	$ 271,327	$ 443,572	$ 449,551	$ 551,269	$ 708,545	$ 805,702	$ 868,599
GAAP EPS (diluted)	$ (2.74)	$ (12.26)	$ (1.17)	$ (4.57)	$ (0.50)	$ (0.45)	$ (2.50)	$ (2.28)	$ (2.85)	$ (3.90)	$ (2.90)	$ 3.14	$ 7.11	$ 11.07	$ 10.68	$ 12.48	$ 15.27	$ 16.54	$ 16.98
Weighted shares outstanding basic and diluted (k)	3,522,607	1,492	5,206	1,701	19,582	25,792	13,070	26,116	29,432	30,559	32,921	36,350	38,167	40,076	42,080	44,183	46,393	48,712	51,148
Margin Analysis:																			
Cost of product sales	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	8%	11%	11%	11%	10%	10%	10%	10%	10%
Product gross margin	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	92%	89%	89%	89%	90%	90%	90%	90%	90%
R&D (GAAP)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	126%	27%	18%	14%	13%	12%	10%	10%	10%
SG&A (GAAP)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	116%	24%	15%	11%	10%	9%	7%	7%	7%
Stock-based compensation expense	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0%	0%	0%	0%	0%	0%	0%	0%	0%
Total operating expense	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	242%	51%	34%	25%	23%	20%	18%	17%	16%
Operating margin	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-150%	38%	55%	64%	67%	70%	72%	73%	74%
Income tax provision	N/A	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	10%	10%	15%	30%	30%	30%	30%	30%
Net margin (GAAP)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-150%	34%	50%	55%	47%	49%	51%	51%	52%
Y/Y change:																			
Total revenue	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	521%	164%	148%	118%	119%	123%	112%	107%
SAGE-547 revenue	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	521%	164%	148%	118%	119%	123%	112%	107%
R&D (GAAP)	N/A	99%	62%	14%	94%	77%	61%	96%	33%	17%	14%	12%	11%	10%	9%	9%	8%	7%	7%
SG&A (GAAP)	N/A	63%	101%	126%	158%	167%	142%	51%	64%	108%	51%	7%	6%	6%	6%	5%	4%	5%	5%
Stock-based compensation expense	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Total operating expense	N/A	90%	71%	33%	110%	96%	79%	83%	40%	42%	30%	10%	9%	8%	8%	7%	6%	6%	6%
Operating income	N/A	90%	71%	33%	110%	96%	79%	83%	40%	42%	-20%	-233%	137%	73%	23%	23%	28%	14%	8%
Net income (GAAP)	N/A	90%	80%	67%	118%	103%	79%	83%	40%	42%	-20%	-220%	137%	63%	1%	23%	29%	14%	8%
GAAP EPS (diluted)	N/A	348%	55%	44%	-83%	-63%	-80%	9%	-25%	-37%	25%	208%	-126%	N/A	-3%	17%	22%	8%	3%
Shares outstanding - GAAP	N/A	-100%	16%	16%	1193%	449%	776%	100%	13%	4%	8%	10%	5%	5%	5%	5%	5%	5%	5%

Source: STRH Research, Company Reports

Sage Therapeutics

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Revenue Build

($thousands, except per share data)

SAGE-547 for super refractory status epilepticus

U.S.

	FY 2013A	FY 2014E	FY 2015E	FY 2016E	FY 2017E	FY 2018E	FY 2019E	FY 2020E	FY 2021E	FY 2022E	FY 2023E	FY 2024E	FY 2025E	FY 2026E
U.S. Population	316,149	319,928	321,470	323,946	326,440	328,954	331,487	334,039	336,611	339,203	341,815	344,447	347,099	349,772
'Incidence of status epilepticus	*0.044%*	*0.044%*	*0.044%*	*0.044%*	*0.044%*	*0.044%*	*0.044%*	*0.044%*	*0.044%*	*0.044%*	*0.044%*	*0.044%*	*0.044%*	*0.044%*
No. U.S. Status epilepticus patients diagnosed per year	140	141	142	143	144	145	147	148	149	150	151	152	153	155
'Incidence hospitalizations due to AE	*0.013%*	*0.013%*	*0.013%*	*0.013%*	*0.013%*	*0.013%*	*0.013%*	*0.013%*	*0.013%*	*0.013%*	*0.013%*	*0.013%*	*0.013%*	*0.013%*
No. of hospitalized SE patients (2nd line SE)	40	40	40	40	41	41	41	42	42	42	43	43	43	44
'% of all SE patients who become refractory to 1st and 1nd line therapy	*23%*	*23%*	*23%*	*23%*	*23%*	*23%*	*23%*	*23%*	*23%*	*23%*	*23%*	*23%*	*23%*	*23%*
No. Refractory status epilepticus (RSE) patients	32	32	32	32	33	33	33	33	34	34	34	34	35	35
% of SE patients that become super refractory	*16%*	*16%*	*16%*	*16%*	*16%*	*16%*	*16%*	*16%*	*16%*	*16%*	*16%*	*16%*	*16%*	*16%*
No. Super refractory status epilepticus (SRSE) patients	22	22	22	22	23	23	23	23	23	23	24	24	24	24
% penetration of SAGE-547	*0%*	*0%*	*0%*	*0%*	*0%*	*7%*	*28%*	*40%*	*55%*	*60%*	*65%*	*68%*	*70%*	*72%*
No. of SRSE patients treated with SAGE-547	*0*	*0*	*0*	*0*	*0*	*2*	*6*	*9*	*13*	*14*	*15*	*16*	*17*	*17*
Gross annual WAC per patient	$ -	$ -	$ -	$ -	$ -	$ 50,000	$ 52,000	$ 54,080	$ 56,243	$ 58,493	$ 60,833	$ 63,266	$ 65,797	$ 68,428
Net annual WAC per patient	$ -	$ -	$ -	$ -	$ -	$ 40,000	$ 41,600	$ 43,264	$ 44,995	$ 46,794	$ 48,666	$ 50,613	$ 52,637	$ 54,743
Total U.S. SAGE-547 sales ($000s)	**$ -**	**$ -**	**$ -**	**$0**	**$0**	**$63,810**	**$267,493**	**$400,479**	**$577,094**	**$659,781**	**$749,077**	**$821,271**	**$886,014**	**$955,079**

E.U.

	FY 2013A	FY 2014E	FY 2015E	FY 2016E	FY 2017E	FY 2018E	FY 2019E	FY 2020E	FY 2021E	FY 2022E	FY 2023E	FY 2024E	FY 2025E	FY 2026E
E.U. Population	501,412	502,102	502,723	503,829	504,938	506,049	507,162	508,278	509,396	510,517	511,640	512,765	513,893	515,024
Incidence of status epilepticus	*0.044%*	*0.044%*	*0.044%*	*0.044%*	*0.044%*	*0.044%*	*0.044%*	*0.044%*	*0.044%*	*0.044%*	*0.044%*	*0.044%*	*0.044%*	*0.044%*
No. E.U. Status epilepticus patients diagnosed per year	221	221	221	222	222	223	223	224	224	225	225	226	226	227
'Incidence hospitalizations due to AE	*0.013%*	*0.013%*	*0.013%*	*0.013%*	*0.013%*	*0.013%*	*0.013%*	*0.013%*	*0.013%*	*0.013%*	*0.013%*	*0.013%*	*0.013%*	*0.013%*
No. of hospitalized SE patients (2nd line SE)	65	65	65	65	66	66	66	66	66	66	67	67	67	67
'% of all SE patients who become refractory to 1st and 1nd line therapy	*23%*	*23%*	*23%*	*23%*	*23%*	*23%*	*23%*	*23%*	*23%*	*23%*	*23%*	*23%*	*23%*	*23%*
No. Refractory status epilepticus (RSE) patients	50	50	50	50	50	50	50	51	51	51	51	51	51	51
% of SE patients that become super refractory	*16%*	*16%*	*16%*	*16%*	*16%*	*16%*	*16%*	*16%*	*16%*	*16%*	*16%*	*16%*	*16%*	*16%*
No. Super refractory status epilepticus (SRSE) patients	35	35	35	35	35	35	35	35	35	35	35	35	35	36
% penetration of SAGE-547	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*4%*	*8%*	*12%*	*15%*	*20%*	*32%*	*38%*	*40%*
No. of SRSE patients treated with SAGE-547	*0*	*0*	*0*	*0*	*0*	*0*	*1*	*3*	*4*	*5*	*7*	*11*	*13*	*14*
Gross annual WAC per patient	$ -	$ -	$ -	$ -	$ -	$ -	$ 52,000	$ 52,000	$ 52,000	$ 52,000	$ 52,000	$ 52,000	$ 52,000	$ 52,000
Net annual WAC per patient	$ -	$ -	$ -	$ -	$ -	$ -	$ 41,600	$ 41,600	$ 41,600	$ 41,600	$ 41,600	$ 41,600	$ 41,600	$ 41,600
Total E.U. SAGE-547 sales ($000s)	**$ -**	**$ -**	**$ -**	**$0**	**$0**	**$0**	**$58,174**	**$116,604**	**$175,291**	**$219,596**	**$293,438**	**$470,534**	**$559,989**	**$590,759**

ROW

	FY 2013A	FY 2014E	FY 2015E	FY 2016E	FY 2017E	FY 2018E	FY 2019E	FY 2020E	FY 2021E	FY 2022E	FY 2023E	FY 2024E	FY 2025E	FY 2026E
ROW reimbursable Population	501,412	503,924	506,195	510,244	514,326	518,441	522,588	526,769	530,983	535,231	539,513	543,829	548,180	552,565
Incidence of status epilepticus	*0.041%*	*0.041%*	*0.041%*	*0.041%*	*0.041%*	*0.041%*	*0.041%*	*0.041%*	*0.041%*	*0.041%*	*0.041%*	*0.041%*	*0.041%*	*0.041%*
No. E.U. Status epilepticus patients diagnosed per year	206	207	208	209	211	213	214	216	218	219	221	223	225	227
'Incidence hospitalizations due to AE	*33%*	*33%*	*33%*	*33%*	*33%*	*33%*	*33%*	*33%*	*33%*	*33%*	*33%*	*33%*	*33%*	*33%*
No. of hospitalized SE patients (2nd line SE)	68	68	68	69	70	70	71	71	72	72	73	74	74	75
'% of all SE patients who become refractory to 1st and 1nd line therapy	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*
No. Refractory status epilepticus (RSE) patients	47	48	48	48	49	49	49	50	50	51	51	52	52	52
% of SE patients that become super refractory	*71%*	*71%*	*71%*	*71%*	*71%*	*71%*	*71%*	*71%*	*71%*	*71%*	*71%*	*71%*	*71%*	*71%*
No. Super refractory status epilepticus (SRSE) patients	34	34	34	35	35	35	35	36	36	36	36	37	37	37
% penetration of SAGE-547	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*1%*	*2%*	*4%*	*5%*	*6%*	*7%*	*8%*	*9%*
No. of SRSE patients treated with SAGE-547	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*1*	*1*	*2*	*2*	*3*	*3*	*3*
Gross annual WAC per patient	$ -	$ -	$ -		$ -	$ -	$ 50,000	$ 50,000	$ 50,000	$ 50,000	$ 50,000	$ 50,000	$ 50,000	$ 50,000
Net annual WAC per patient	$ -	$ -	$ -	$ -	$ -	$ -	$ 40,000	$ 40,000	$ 40,000	$ 40,000	$ 40,000	$ 40,000	$ 40,000	$ 40,000
Total ROW SAGE-547 sales ($000s)	**$ -**	**$ -**	**$ -**	**$0**	**$0**	**$0**	**$7,071**	**$28,509**	**$57,474**	**$72,417**	**$87,595**	**$103,012**	**$118,670**	**$134,572**

Total WW SAGE-547 sales ($000s)	**$ -**	**$ -**	**$ -**	**$0**	**$0**	**$63,810**	**$332,738**	**$545,591**	**$809,859**	**$951,793**	**$1,130,111**	**$1,394,818**	**$1,564,672**	**$1,680,410**

Source: STRH Research, Company Reports

Company Description

SAGE Therapeutics, Inc. is a biopharmaceutical company focused on developing and commercializing novel medicines to treat life threatening, rare central nervous system disorders. Its lead program SAGE-547 is in clinical development for super-refractory status epilepticus and is the first of several compounds the company is developing in its portfolio of potential seizure medicines. The company's robust chemistry platform has generated multiple new compounds that target the GABA-A and NMDA receptors, which are well-characterized with regard to their role in many psychiatric and neurological disorders.

Investment Thesis

SAGE is positioning itself as a premier orphan play, focused on central nervous system (CNS) diseases of high unmet need, with well-defined molecular characteristics and likely short drug development timelines. SAGE is one of the few players in the CNS space, a field with significant unmet need – that has been historically difficult to tackle in drug development. The company recently went public, with the key strategy to use its broad platform (chemical modulators of brain molecules) to focus on drug development for CNS indications that are: 1) well-defined from a molecular perspective, and 2) have short drug development timelines (small numbers of patients, short clinical trial duration). SAGE's lead drug candidate is SAGE-547, a modulator of the neural gamma-amino butyric acid (GABA) receptor. SAGE-547 is about to enter pivotal testing in mid-2015 for super-refractory status epilepticus, a rare type of epilepsy characterized by persistent seizures (>24 hours), in spite of treatment with multiple rounds of anesthetics. The company has two second generation molecules in the wings (SAGE-217 and SAGE-689) expected to enter the clinic in late-2015, as well as a platform of early stage modulators (N-Methyl-D-aspartic acid receptor, NMDA) of cellular brain function, slated to expand the epilepsy/CNS orphan disease franchise.

Valuation and Risks

We arrive at our price target of $67 by means of a sum-of-the-parts discounted cash flow analysis, which ascribes $53.49/share to SAGE-547 U.S. sales, $8.76 to SAGE-547 E.U. sales, $0.62 to SAGE-547 ROW sales, and $4.38/share to cash. We assign SAGE-547 in a probability of success of 58% in the U.S., 25% in the E.U., and 25% in ROW. We assume a discount rate of 12% and a 1% terminal growth rate to SAGE-547 in the U.S. and the E.U., and no terminal value for SAGE-547 in ROW.

Risks:

- **Clinical Risk:** SAGE-547 may fail to repeat its 71-78% response rate from Phase II trials and eIND use in a pivotal trial. It is possible that both the Phase II and eIND patients had a higher chance of recovering from SRSE than the ~30% chance quoted by SAGE, and of the 30-50% chance quoted by our physician consultants. This could be due to the inclusion/exclusion criteria used in Phase II, or another reason altogether. Although preclinical rationale for SAGE-547 is suggestive that the compound could have utility in ET and PPD, the benefit in animals may not translate well in humans. Finally, although they have similar putative mechanisms of action, there is some chance that proof-of-concept for SAGE-547 does not read through to other GABA modulators SAGE-689 and SAGE-217.
- **Regulatory risk:** The FDA may require more rigorous clinical trials than we anticipate. We believe that SAGE's expected Phase III endpoint of being seizure-free after the patient is weaned from both general anesthesia and SAGE-547 should be appropriate. However, the FDA may ask for a randomized controlled study, which may be difficult to set up given the variability in standard of care among different treatment centers. Longer term follow-up could be required, for example an endpoint such as % of patients who are seizure free 1 month after wean. We expect clarity on this endpoint in Q1 2015, when SAGE communicates the results of their end-of-Phase II meeting with FDA.
- **Commercial risk:** SAGE plans to target the relatively small number of ICUs (~900 hospitals in the U.S.) and epilepsy treatment centers (~200 in the U.S.), where SRSE patients are treated. E.U. has a comparable number of centers. The remains a commercial risk (albeit low) that SAGE is unable to effectively reach these patients.
-

Competitive Risk: Although we are not aware of any significant competitive drugs in development for status epilepticus (SE), Marinus Pharmaceuticals (MRNS) is developing ganaxolone, a similar GABA-receptor targeted agent (although restricted to hitting the synaptic receptors), for the treatment of other forms of epilepsy and Fragile X syndrome. Although ganaxolone is unlikely to be approved for SE without clinical trials in that population, if the drug does become available it could be used off-label.

- **Financial risk:** Given the expenses associated with conducting clinical trials and launch of the product, we anticipate that SAGE may have to issue additional equity through follow-on offerings

Companies Mentioned in This Note

Marinus (MRNS, $10.96, NR)
GW Pharmaceuticals (GWP-LON, $4.17, NR)
H.Lundbeck (HLUYY, $21.78, NR)
Isis Pharmaceuticals, Inc. (ISIS $71.28 NR)
Biogen Idec Inc. (BIIB $357.53 NR)
Santhera Pharmaceuticals Holding AG (SANN-SWX $92.00 NR)
AstraZeneca PLC Sponsored ADR (AZN $70.69 NR)
Johnson & Johnson (JNJ $102.20 NR)
Ranir - private
Lander - private

Analyst Certification

I, Salveen Richter , hereby certify that the views expressed in this research report accurately reflect my personal views about the subject company(ies) and its (their) securities. I also certify that I have not been, am not, and will not be receiving direct or indirect compensation in exchange for expressing the specific recommendation(s) in this report.

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SunTrust Robinson Humphrey, Inc. makes a market in the following companies at the time of this report: BMRN, SAGE, SAGE-US, SHPG

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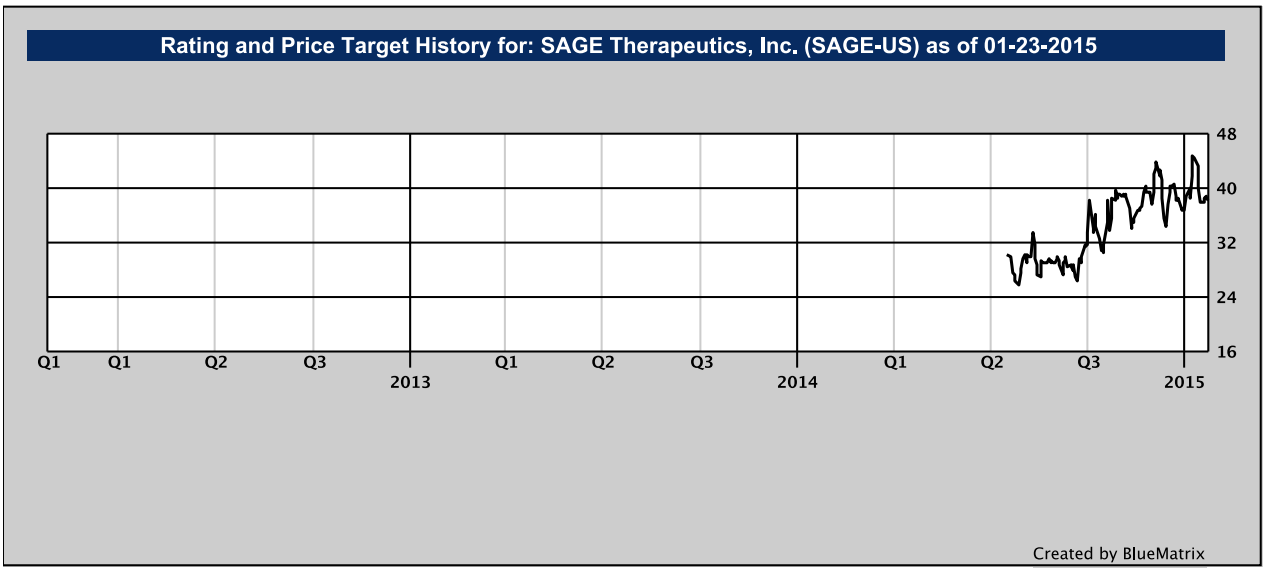
Rating and Price Target History for: SAGE Therapeutics, Inc. (SAGE-US) as of 01-23-2015
48
40
32
24
16
Q1
Q1
Q2
Q3
2013
Q1
Q2
Q3
2014
Q1
Q2
Q3
2015
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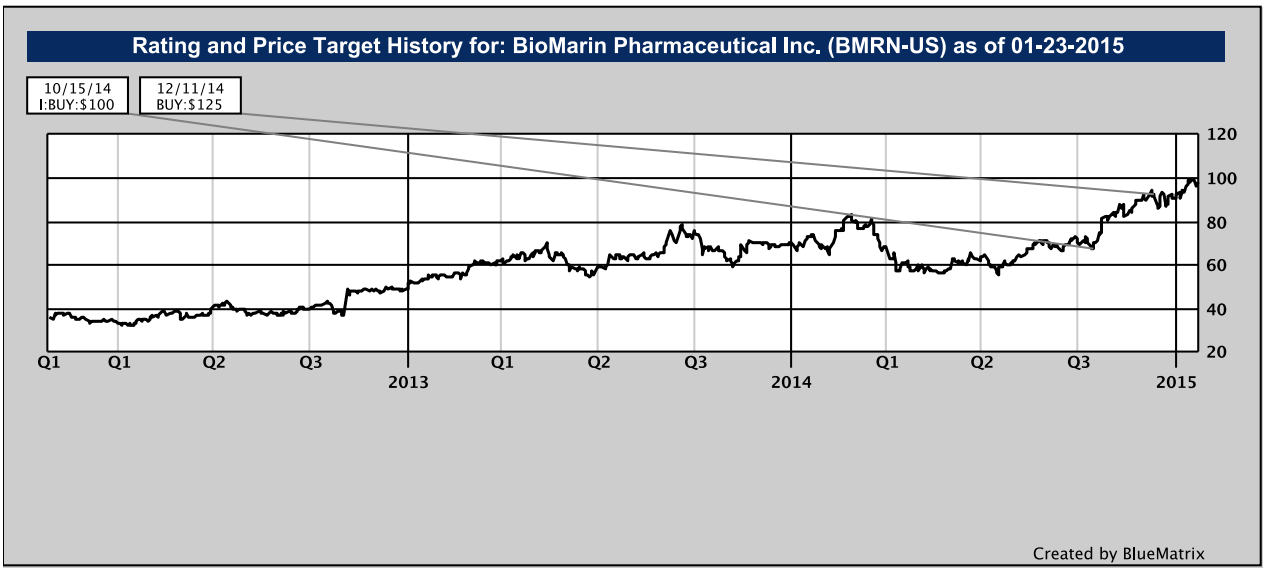
Rating and Price Target History for: BioMarin Pharmaceutical Inc. (BMRN-US) as of 01-23-2015
10/15/14
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12/11/14
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120
100
80
60
40
20
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Q2
Q3
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Q1
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Q3
2014
Q1
Q2
Q3
2015
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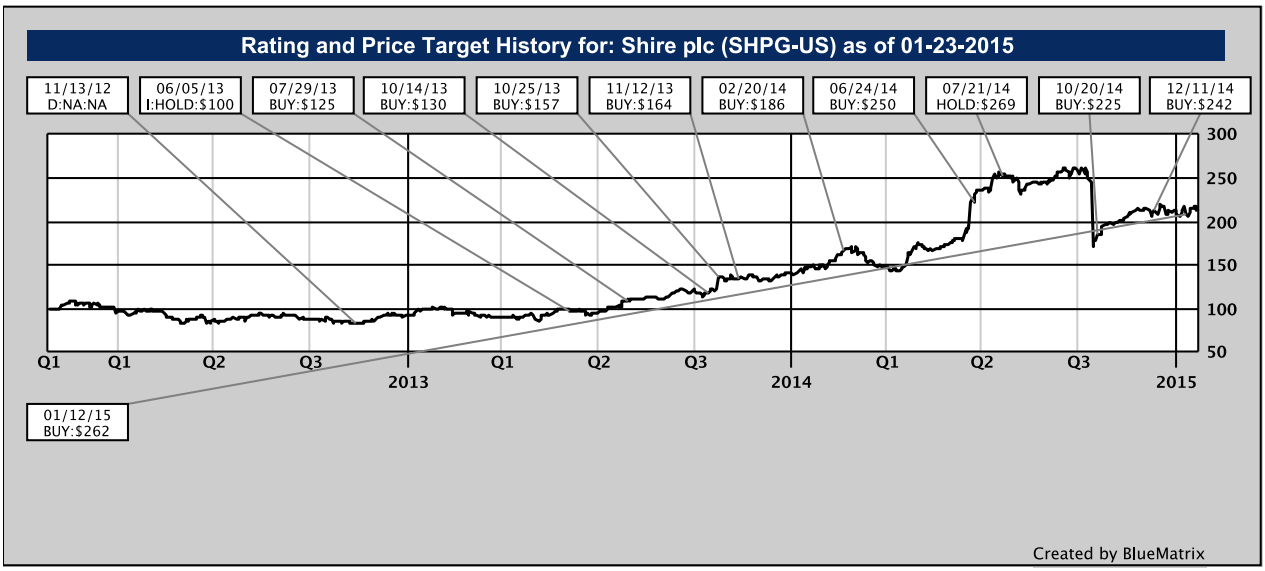

STRH Ratings System for Equity Securities

3 designations based on total returns* within a 12-month period**

- **Buy** – total return ≥ 15% (10% for low-Beta securities)***
- **Reduce** – total return ≤ negative 10% (5% for low Beta securities)
- **Neutral** – total return is within the bounds above
- **NR** – NOT RATED, STRH does not provide equity research coverage
- **CS** – Coverage Suspended

*Total return (price appreciation + dividends)
**Price targets are within a 12-month period, unless otherwise noted
***Low Beta defined as securities with an average Beta of 0.8 or less, using Bloomberg's 5-year average Beta

Legend for Rating and Price Target History Charts:
D = drop coverage
I = initiate coverage
T = transfer coverage

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Coverage Universe			Investment Banking Clients Past 12 Months		
Rating	**Count**	**Percent**	**Rating**	**Count**	**Percent**
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Neutral	253	46.85%	Neutral	42	16.60%
Sell/Reduce	11	2.04%	Sell/Reduce	2	18.18%

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