SAGE Therapeutics, Inc. (SAGE)

Next-Up: Update from End-of-P2 FDA Meeting in March

Buy

Price Target: $67.00
Prior: $67.00

Price (Mar. 11, 2015)	$45.76
52-Wk Range	$45.76-$25.86
Market Cap ($M)	$1,181
ADTV	163,679
Shares Out (M)	25.8
Short Interest Ratio/% Of Float	7.5%
TR to Target	46.4%

Cash Per Share	$4.12
Total Debt	$0.0
Cash And Equivalents ($M)	$127.8

	2014E	2015E		2016E	
		Curr.	Prior	Curr.	Prior
Revenue ($M)					
FY	0	0	0	0	0
EPS Adjusted					
FY	(1.67)A	(2.52)	(2.52)	(2.86)	(2.86)
P/E	NM	NM		NM	
Consensus Rev					
FY	0	0	0	0	0
Consensus EPS Adjusted					
FY	(2.51)A	(2.09)	(2.09)	(2.44)	(2.44)
FYE Dec					

What's Incremental

SAGE is slated to meet with the FDA in Q1/15 to discuss the pivotal study design for SAGE-547 in super refractory status epilepticus. The key question is whether this trial would be single arm or randomized controlled. We spoke with management and believe there are advantages to either outcome, described below. Per SAGE, the study duration could be 1-2 years (100-200 pts.); we conservatively model the higher end of this range. Shorter completion timelines would be upside to our estimates. Further, we look to mid-15 proof-of-concept for 547 in ET and PPD and YE15 disclosure of the NMDA program.

Visibility from the Q1/15 meeting with the FDA represents a catalyst for SAGE. To date, SAGE has generated clinical data for SAGE-547 in super refractory status epilepticus (SRSE), continuous seizures, which is viewed as impressive by key opinion leaders (KOLs). The ~71% response rate in the Phase I/II study (N=17 patients) and the emergency use program (N=9) compare with a 22-43% historical response rates in SRSE per our review of literature and KOL feedback. A pivotal trial for SAGE-547 in SRSE is slated to begin in mid-15 and incorporate FDA feedback. Ahead of SAGE's End-of-Phase II meeting with the agency, we believe two scenarios could play out for the pivotal trial design: **1) the agency requests that a randomized controlled trial (RCT) is conducted to support SAGE-547 registration for SRSE or 2) the FDA suggests SAGE conduct a single arm study and use historical data for comparison.**

We view management's guidance for a pivotal study design as sensible/conservative. First, variability around the 100-200 patient targeted enrollment is driven by a potential size of the safety database requested by the FDA. Second, the 1-2 year duration (~5 days of dosing) entails conservative assumptions for onboarding (rate limiting step) of the 60-80 targeted clinical trial sites. 17 sites are currently involved in the Phase I/II study and would require re-contracting and additional Institutional Review Boards (IRB) agreements, though likely quick onboarding. We anticipate SAGE will announce the outcome of this meeting in March, with clarity on the product's registrational path. We conservatively model for the higher end of the 1-2 year duration guidance.

Agreement with the FDA on a single arm study would be upside to our expectations and likely viewed as positive by investors. Hospital IRBs may decide that it is unethical to compare SAGE-547 against the standard of care (SoC), given that SRSE patients by definition have already failed to achieve SE resolution with most if not all currently-available therapies, and in light of the SAGE-547 clinical results to date. Thus, the FDA could

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SEE PAGE 4 FOR REQUIRED DISCLOSURE INFORMATION

agree that an open label single arm pivotal trial of SAGE-547 be sufficient for registration. In this scenario, historical patient data would be gathered concurrently from the same sites. The limitations of this approach are: 1) absent a comparator arm, all safety observations (expected for critically ill SRSE patients) would be contained in a potential SAGE-547 label, and 2) identifying comparable historical data (matching baseline characteristics, previous therapy and duration of follow-up) is a complex process. Per management, efforts to gather a robust historical dataset will take place in parallel to the trial, and may eventually enhance the company's commercial relationship to these clinical sites. **We believe investors would view this design as a positive for SAGE, with a potentially lower degree of clinical risk.**

An RCT would be in line with our expectations and would strengthen a potential label. KOLs we spoke with note that, for an RCT, a control regimen would most likely entail maintenance of medically-induced coma with SoC general anesthetics (e.g. propofol, midazolam, thiopental), followed by attempts to wean patients. The treatment arm would entail addition of SAGE-547 to the SoC followed by wean attempts. Such a design is in line with our expectations regarding study duration and targeted number of patients (towards the higher end of 100-200 patients and 1-2 years). We believe a potential label for SAGE-547 would be significantly strengthened by RCT data. Given the presence of a comparator arm for safety observations, we anticipate the number of serious adverse events listed in a potential SAGE-547 label to be materially lower than in the single arm scenario.

We are looking forward to additional catalysts for SAGE starting in mid-2015. In addition to SRSE (exp. pivotal trial start in mid-15), SAGE-547 is also being used as a probe molecule for essential tremor and post-partum depression (indications whereby its mode action appears well-suited to modulate the underlying cause of the disease). Final results from the ongoing Phase I/II study of 547 in SRSE are slated to report out by mid-2015, potentially presented as a Late Breaker abstract at the American Academy of Neurology (AAN) meeting, Apr 18-25, Washington DC) or at the London-Innsbruck Colloquium on Status Epilepticus (Apr 9-11, London). Two additional products are on track to enter the clinic by YE15: SAGE-689 as adjunctive i.v. second-line therapy for RSE, and SAGE-217 in an orphan epilepsy. Another program targeting the neural NMDA receptor could also be announced in 2015 in an orphan indication.

Sage Therapeutics

(NASDAQ: SAGE)

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Consolidated Income Statement

($thousands, except per share data)	FY 2012A	FY 2013A	FY 2014A	Mar Q1 2015A	Jun Q2 2015A	Sep Q3 2015E	Dec Q4 2015E	FY 2015E	FY 2016E	FY 2017E	FY 2018E	FY 2019E	FY 2020E
Revenue													
SAGE-547	$ -	$ -	$ -	-	-	-	-	$ -	$ -	$ -	$ 63,810	$ 332,738	$ 545,591
Total Revenue	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 63,810	$ 332,738	$ 545,591
COGS	-	-	-	-	-	-	-	-	-	-	5,105	36,601	60,015
Gross profit	-	-	-	-	-	-	-	-	-	-	58,705	296,137	485,576
Operating expense													
R&D (GAAP)	7,229	14,357	24,100	9,542	10,559	12,155	14,546	46,802	60,221	70,224	80,334	90,211	100,260
SG&A (GAAP)	2,402	3,922	9,710	3,812	4,044	5,157	5,544	18,557	23,556	48,910	74,002	79,043	84,056
Total operating expense	9,631	18,279	33,810	13,354	14,603	17,312	20,090	65,359	83,777	119,134	154,336	169,254	184,316
Operating income (loss)	**(9,631)**	**(18,279)**	**(33,810)**	**(13,354)**	**(14,603)**	**(17,312)**	**(20,090)**	**(65,359)**	**(83,777)**	**(119,134)**	**(95,631)**	**126,883**	**301,260**
Interest Income (expense), net	-	1	8	4	4	5	4	17	34	54	58	91	212
Other income (expense), net	(1)	(3)	(9)	-	-	-	-	-	-	-	-	-	-
Total Other Income	(1)	(2)	(1)	4	4	5	4	17	34	54	58	91	212
Income before income taxes	(9,632)	(18,281)	(33,811)	(13,350)	(14,599)	(17,307)	(20,086)	(65,342)	(83,743)	(119,080)	(95,573)	126,974	301,472
Provision for income taxes	-	-	-	-	-	-	-	-	-	-	-	12,697	30,147
Net gain (loss)	**(9,632)**	**(18,281)**	**(33,811)**	**(13,350)**	**(14,599)**	**(17,307)**	**(20,086)**	**(65,342)**	**(83,743)**	**(119,080)**	**(95,573)**	**114,276**	**271,325**
Accretion of redeemable convertible preferred stock	(4)	(7)	(2,294)										
Net gain (loss) applicable to common shareholders	**$ (9,636)**	**$ (18,288)**	**$ (36,105)**	**$ (13,350)**	**$ (14,599)**	**$ (17,307)**	**$ (20,086)**	**$ (65,342)**	**$ (83,743)**	**$ (119,080)**	**$ (95,573)**	**$ 114,276**	**$ 271,325**
GAAP EPS (diluted)	**$ (2.74)**	**$ (12.26)**	**$ (1.67)**	**$ (0.52)**	**$ (0.56)**	**$ (0.67)**	**$ (0.77)**	**$ (2.52)**	**$ (2.86)**	**$ (3.92)**	**$ (2.92)**	**$ 3.16**	**$ 7.15**
Weighted shares outstanding basic and diluted (k)	3,522,607	1,492	21,574	25,736	25,865	25,994	26,124	25,930	29,242	30,368	32,719	36,139	37,946
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%
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%
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%
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%
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%
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%
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%
Income tax provision	N/A	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	10%	10%
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%
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%
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%
R&D (GAAP)	N/A	99%	68%	129%	141%	84%	63%	94%	29%	17%	14%	12%	11%
SG&A (GAAP)	N/A	63%	148%	136%	124%	80%	62%	91%	27%	108%	51%	7%	6%
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
Total operating expense	N/A	90%	85%	131%	136%	83%	63%	93%	28%	42%	30%	10%	9%
Operating income	N/A	90%	85%	131%	136%	83%	63%	93%	28%	42%	-20%	-233%	137%
Net income (GAAP)	N/A	90%	97%	118%	88%	76%	62%	81%	28%	42%	-20%	-220%	137%
GAAP EPS (diluted)	N/A	348%	-86%	-56%	-88%	32%	59%	-51%	-14%	-37%	26%	208%	-126%
Shares outstanding - GAAP	N/A	-100%	1346%	394%	1421%	33%	2%	20%	13%	4%	8%	10%	5%

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

SAGE Therapeutics, Inc. (SAGE, $45.76, Buy)
Marinus (MRNS, $10.00 , NR)

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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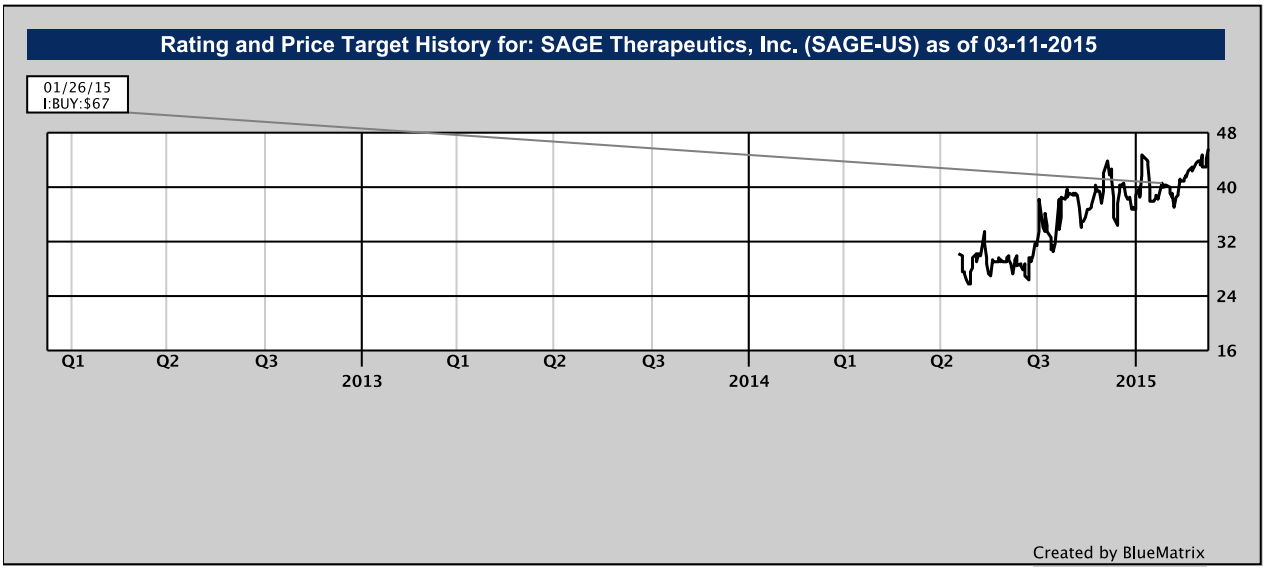

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*Total return (price appreciation + dividends)
**Price targets are within a 12-month period, unless otherwise noted
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Legend for Rating and Price Target History Charts:
D = drop coverage
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