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OUTPERFORM

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LEERINK

Reason for report:

PROPRIETARY INSIGHTS

SAGE THERAPEUTICS, INC.

Specialist Thoughts, Deep Dive on SAGE-547 in SRSE, Tremor and PPD. PT to $93

• **Bottom Line:** On the heels of full SAGE-547 phase I/II SRSE (Super Refractory Status Epilepticus) data and ahead of pilot study readouts in essential tremor (ET) and postpartum depression (PPD), we spoke with multiple MEDACorp KOLs and performed a deep dive into the broader applicability of SAGE's synaptic/extrasynaptic GABA-R allosteric modulation platform. Based on the robust, 77% rate in the full phase I/II data set, MEDACorp specialists expect '547 to be used in the vast majority of SRSE patients, as well as upstream of SRSE in individuals who have not yet received anesthesia. Meanwhile, with a strong clinical rationale but little priced into the stock, we see a favorable risk/reward ahead of ET/PPD data in mid-2015. **Reit. OP. PT to $93 from $70 on an increase in SRSE ests and a small addition to pipeline sales.**

• **With a 77% response rate in the ph. I/II, specialists expect SAGE-547 to be used in the vast majority of SRSE patients** as well as upstream from SRSE in the status epilepticus treatment paradigm. We are now modeling (1) higher peak-penetration in SRSE - 70% from 55% and (2) 5% penetration in refractory status, and see pot'l upside should a SAGE-689 show pot'l in 2nd line status.

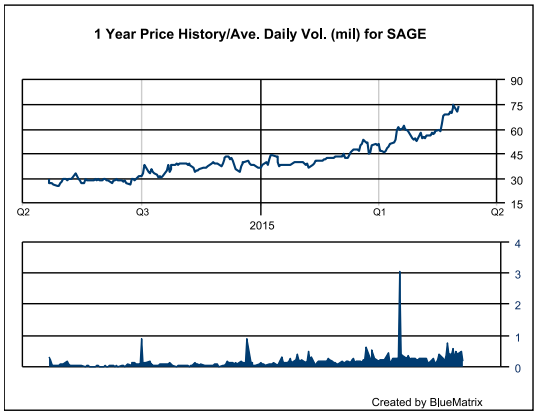
• **KOLs see a strong clinical rationale for SAGE-547 in PPD.** Specialists are intrigued by the clinical potential of SAGE-547 in depression and cite a long-standing hypothesis that the onset of depression after childbirth may be driven by large drops in progesterone/ allopregnanolone and the resultant impact on GABA. Within we highlight 8 papers that posit a connection between ALLO, extra-synaptic $GABA_A$-Rs and PPD onset in preclinical models and small samples of human subjects. Given that the PPD study is small (N=10) and open-label but because the efficacy endpoint is captured quickly (4 days), specialists believe a 30%-40% benefit on the HAM-D-17 (depression scale) and/or a strong effect on question 3 (suicidality) would be clinically meaningful.

• **Based on '547's impact on synaptic $GABA_A$-R, we believe the tremor study is likely to show at least a modest signal -** key will be (1) how much stronger this efficacy is than Gx benzos and (2) whether any increased potency comes w/ poor tolerability**.** After beta-blockers, benzodiazepines are generally used 2nd-line in ET but are often limited by dose-limiting sedation. While mechanistically '547 should work at least as well as benzos, study success may hinge on patient selection (study N=24), the degree to which extra-synaptic $GABA_A$-Rs are expressed and "druggable" during ET, and whether or not any augmented GABAergic effect will be met with more sedative adverse events.

• **While 0, 1 or 2 studies may be successful, we believe the range of stock up/down on the data is +50%/-5% to -10%, with upside if either trial hits.** Heavily risk-adjusted sales in ET/PPD could be worth ~$15-$30/share. If both studies hit we'd expect stock move to overshoot this.

Key Stats:	**(NASDAQ:SAGE)**
S&P 500 Health Care Index:	**862.71**
Price:	**$73.81**
Price Target:	$93.00 from $70.00
Methodology:	DCF analysis with 11% discount rate
52 Week High:	$76.25
52 Week Low:	$24.25
Shares Outstanding (mil):	30.3
Market Capitalization (mil):	$2,236.4
Book Value/Share:	$2.45
Cash Per Share:	$7.45
Dividend (ann):	$0.00
Dividend Yield:	0.0%

Shares Outstanding (mil): Fully diluted shares outstanding estimated as of 3Q15E
Cash Per Share: Cash/diluted shares 2Q15



Dec Yr	1Q	2Q	3Q	4Q	FY Rev	1Q	2Q	3Q	4Q	FY EPS	P/E
2014A	0.0	0.0	0.0	0.0	0.0	($3.71)	($4.57)	($0.50)	($0.48)	($1.67)	NM
2015E	0.0A	0.0	0.0	0.0	0.0	($0.66)A	($0.67)	($0.68)	($0.71)	($2.72)	NM
2016E	--	--	--	--	0.0	--	--	--	--	($3.69)	NM

Source: Company Information and Leerink Partners LLC Research
GAAP EPS.

INVESTMENT THESIS

We rate SAGE shares Outperform. SAGE Therapeutics (NASDAQ: SAGE) is a neuroscience company started by an experienced team of R&D leaders and CNS specialists focused on developing medicines to treat life-threatening, rare neurological disorders. SAGE's lead product, SAGE-547, is in clinical development for super-refractory status epilepticus (SRSE) and is the first of many compounds the company is developing in its positive allosteric modulation (PAM) portfolio. SAGE-547 is a PAM of both synaptic and extra-synaptic $GABA_A$ receptors that rapidly advanced into Phase I/II clinical development in early 2014. The robust clinical potential of '547 was demonstrated under an emergency Investigational New Drug (IND) program in which 5 out of 7 SAGE-547-treated SRSE patients (each of whom had spent over 30 days in the ICU) were successfully weaned out of a medically induced coma. These data were corroborated by final results from a phase I/II study, in which 77% of SAGE-547-treated SRSE patients have been weaned off anesthesia while on '547 therapy. While perfect natural history data is lacking in SRSE, published literature suggests that SRSE patients are weaned successfully in ~30% of cases. We see SAGE as a potential platform company, and upcoming SAGE-547 data readouts in postpartum depression and essential tremor will test the relevance of extra-synaptic $GABA_A$-Rs in other indications. Beyond '547, SAGE is developing a seizure franchise of advanced next generation compounds of novel $GABA_A$ allosteric modulators for the treatment of SE and other forms of seizure and epilepsy. SAGE-689 is currently in preclinical development for status epilepticus and is expected to enter a Phase I trial in 2015. In addition, SAGE-217 is being developed as an oral therapy for orphan genetic epilepsies such as Dravet syndrome and Rett. We believe SAGE shares are poised to appreciate as de-risking clinical catalysts are realized for the company's lead product and allosteric modulation platform.

SPECIALIST THOUGHTS AND DEEP DIVE ON SAGE-547 SRSE, TREMOR AND PPD

With a 77% response rate in the phase I/II study, specialists expect SAGE-547 to be used in the vast majority of SRSE patients as well as upstream from SRSE in the status epilepticus treatment paradigm. Similar to other companies who've to date only validated their lead product through the generation of open-label data, investors continue to debate the true "placebo" or "natural history" response rate off which SAGE-547's 77% success should be compared. However, with 22 patients treated in the phase I/II, 7 more serious patients treated in the emergency use program and a high response rate in very poor prognosis SRSE patients (for whom the literature suggests a resolution rate of ~33%), specialists are relatively confident that '547 is harnessing a novel GABAergic mechanism that is not employed by any available therapies. Moreover, SRSE itself is defined and distinguished from RSE by the fact that a "super-refractory" patient has failed at least one wean attempt with general anesthesia (GA), akin to "trying to push the reset button" in a seizing patients brain. Understandably, specialists would prefer to avoid ever using neuroanesthesia in a status patient, and some expect to immediately adopt '547 ahead of GA in the status epilepticus treatment paradigm, pending the ability to obtain reimbursement. Based on this relatively bullish KOL feedback, we are now modeling (1) higher peak-penetration in SRSE - 70% from 55% and (2) 5% penetration in refractory status, and see potential upside SAGE-689 show potential in 2nd line status epilepticus. The changes to our

model increase our US/ROW 2024E SAGE-547 gross (non-risk adjusted) revenue estimates to ~$1.3B/~$640MM from ~$1B /~$630MM.

Meanwhile, KOLs see a strong clinical rationale for SAGE-547 in PPD, but will be looking for a relatively large effect given that the study is small and lacks a placebo arm. Specialists are intrigued by the clinical potential of SAGE-547 in depression and cite a long-standing hypothesis that the onset of depression after childbirth may be driven by large drops in progesterone/allopregnanolone and the resultant impact on GABA. We were able to dig up multiple articles that posit a connection between allopregnanolone (ALLO), extra-synaptic $GABA_A$-receptors and both PPD and PMD (post-menstrual depression). Given that the PPD study is small (N=10) and open-label but because the efficacy endpoint is captured quickly (4 days), specialists believe a 30%-40% benefit on the HAM-D-17 (slightly less than the benefit of SSRIs after 2 weeks) and/or a strong effect on question 3 (suicidality) would be clinically meaningful and warrant further research. While PPD specifically currently represents upside to our model, we believe a positive study could lead to the addition of $100-$200MM in risk-adjusted sales to our model (~$1B opportunity at a 10-20% probability-of-success) which would increase our PT by ~$7-15/share.

Based on '547's impact on synaptic $GABA_A$-R we believe the tremor study is likely to show a signal – key will be (1) how much stronger this efficacy is than generic benzos and (2) whether or not increased any potency comes at the cost of worsened tolerability. After beta-blockers, benzodiazepines are generally used 2nd-line in ET but are often limited by either diminishing efficacy (i.e., tolerance) or dose-limiting sedation. It will be important for SAGE-547 to either have a stronger effect than benzos or show efficacy in treatment-failures as benzodiazepines that are indicated for ET are already generic. Studies of benzodiazepines such as Xanax, Ativan and Klonopin have generally shown efficacy in reducing tremor burden and an especially robust effect in patients who report comorbid anxiety. However, some studies of benzos in ET have not shown a statistically significant benefit, especially when higher doses were examined which can confer temporary symptom control but ultimately lead to high sedation rates and drug discontinuation. The potential sedative properties of SAGE-547 or any of SAGE's $GABA_A$-R synaptic/extra-synaptic allosteric modulating agents is not yet well understood, and mechanistically there are arguments (reviewed on page 7) that suggest a better or relatively more challenging tolerability profile. Like PPD, ET represents a very large market opportunity: with ~1MM patients on pharmacotherapy in the US, a ~$10k/year drug that captures 8% market share would generate almost $1B in sales, and the addition to heavily risk adjusted sales could add $7-$15/share to our PT.

For the stock we see multiple scenarios which hinge on (1) whether or not 0, 1 or 2 studies succeed and (2) SAGE-547's safety/tolerability profile, specifically with respect to rates of sedation. In the table below we outline our view on the upside/downside for SAGE shares on various data readouts. In a scenario in which both studies hit and safety looks good, we'd expect the stock to be up over ~50% based off not only the addition of ET/PPD sales to the model but also increased bullishness on the broad applicability of the SAGE's $GABA_A$-R allosteric modulation platform. While we believe little if any credit exists for ET/PPD specifically in consensus SAGE models, we'd expect minor-to-modest downside on study failures (the magnitude of which is likely to depend on safety) as it removes a potential near-term upside driver and also could pose are read-through onto other programs. Fortunately, we believe that a safety signal would have little relevance to the SRSE program (the vast majority of the market's value for SAGE shares) where

acute CNS adverse events are largely irrelevant as patients concurrently receive GA. The stock impact of a scenario in which one study is a success on efficacy but uncovers a safety/tolerability concern is somewhat more challenging to handicap; we believe this could lead to the addition of some ET/PPD sales to the model (especially in serious "refractory" patients) and potentially more bullishness on the applicability of the pipeline, however it may also increase perceived clinical risk for non-SRSE programs.

Potential Stock Sensitivity on ET and PPD Study Data Readouts

	Favorable Safety/Tolerability Profile	Dose Limiting Safety/Tolerability
Both Studies Show Strong Efficacy	$35+	$5 to $15
One Study shows Strong Efficacy	$7 to $15	$0 to $5
0 Studies Show Efficacy	-$2 to -$4	-$7 to -$10

Source: Leerink Partners Estimates

Perhaps most important to the Street's long-term view on the potential of the stock, the tremor and PPD data may shed light on two key questions with important implications for the SAGE platform:

1) **When, where and why are extra-synaptic $GABA_A$-receptors expressed and therapeutically relevant?** First and foremost, we, like many investors, believe the SAGE platform's magnitude of differentiation from currently available benzodiazepines will likely be dictated by the importance and/or "drugability" of extra-synaptic $GABA_A$ receptors in various CNS diseases. If extra-synaptic $GABA_A$-Rs are only expressed during status epilepticus or bouts of continuous seizure, it's possible that SAGE-547 (or any other $GABA_A$ allosteric modulator) might only be equally effective as benzodiazepines in other neurological ailments. Should SAGE-547 show more robust efficacy than benzodiazepines in tremor patients, or efficacy in ET patients who've already failed benzodiazepines, this would render us considerably more confident that extra-synaptic $GABA_A$-Rs may be relevant player in multiple therapeutic areas. Interestingly, multiple publications (reviewed in the next section) suggest that extra-synaptic $GABA_A$-Rs may have a role multiple disease states including PPD, depression, anxiety and seizure. Perhaps most interesting for SAGE is the data generated for Gaboxadol, a MRK (MP)/Lundbeck drug that directly agonized extra-synaptic $GABA_A$-Rs and was being studied for insomnia. In patients with sleep difficulties, daily Gaboxadol therapy was able to precipitate statistically significant increases in slow wave sleep, reductions in sleep latency, and mean total sleep time. While insomnia patients may or may not be representative of individuals with other central nervous system (CNS) ailments, we see this patient population as relatively more similar to PPD and ET patients than the SRSE population, as in the latter cohort there are many confounding variables to consider.

2) **Will the concurrent allosteric modulation of synaptic and extra-synaptic GABA-R be safe and well tolerated?** While SAGE-547 has generated a robust efficacy data set in SRSE, it remains somewhat challenging to assess fully the drug's safety/tolerability profile since hospitalized status epileptic patients suffer from many different ailments (HIV, brain trauma, epilepsy) and are concurrently treated with multiple neurologically-active therapies, including GA. As we stated above, there is a mechanistic rationale to

believe that SAGE-547 and the concurrent allosteric modulation of synaptic and extra-synaptic $GABA_A$-R could be more or less sedative than just synaptic $GABA_A$-R modulation with benzos. On the one hand, specialists are cautious that increasing GABAergic neuronal firing via any medium may have a more anesthetic effect on patients; SAGE-547 is a potent modulator of synaptic-$GABA_A$ receptors, so any impact on the extra-synaptic system should theoretically be additive to the GABAergic effect. However, literature suggests that all types of allosteric modulation of $GABA_A$-R are not equal: extra-synaptic receptors allegedly induce tonic inhibition, versus short lasting, "plastic" inhibition by synaptic $GABA_A$-Rs. We think the safety experiences of Gaboxadol and Ganaxalone provide evidence for the bear and bull cases for SAGE-547 respectively. While Gaboxadol showed strong efficacy and favorable tolerability in sleep, the program was discontinued pre-NDA filing when an FDA-required safety study in patients with a history of drug addiction showed the incidence of hallucinations at very high (supra-therapeutic) doses. While it's possible this risk could have been managed through scheduling or REMS (Risk Evaluation and Mitigation Strategies), it rendered Gaboxadol less competitive in a mass market area with little tolerability for safety concerns such as sleep. Gaboxadol may not be a perfect comp for SAGE-547 however since it directly agonizes extra-synaptic $GABA_A$-Rs, whereas SAGE-547 is a positive allosteric modulator. Conversely, Marinus' (MRNS, NR) experience with Ganaxalone has been very encouraging for SAGE-547. Ganaxalone is a (albeit potentially less potent) modulator of synaptic and extra-synaptic $GABA_A$-Rs being studied for partial onset seizures and other orphan epilepsies. In >1,000 patients treated to date the drug has shown a very favorable safety profile with low discontinuation rates and only modest increases in sedation and fatigue.

While Gaboxadol Showed an Unexpected Safety Signal at Supra-Therapeutic Doses, Ganaxalone Phase II Safety Data is Encouraging for SAGE-547

		Ganaxolone n=98	Placebo n=49
		% Incidence	
	SAEs	5	8
	% Subjects w/ AE	84	78
	D/C due to AEs	7	6
Adverse Events >5% for Ganaxolone (Double Blind Study)	Dizziness	16	8
	Fatigue	16	8
	Sleepiness	13	2
	Injury	17	22
	Headache	8	12
	Abnormal Coordination	6	6
	Convulsion (seizure)	5	8
	Nasopharyngitis	5	10
	Fall	5	12
Safety Tests - Double Blind and Open Label Study	No trends or clinically meaningful changes in ECG, chemistry or vital signs, no evidence of weight gain		
	Safety Profile was consistent in long-term extension to Phase 2		

Source: Company Presentations

If a meaningful signal is observed in either the tremor or PPD studies, SAGE expects to address one or both of these unmet needs with a follow-on oral compound, as the company has a library of >1500 $GABA_A$-R PAMs (positive allosteric modulation) that operate via the same mechanism-of-action as '547 but have pharmacokinetic (PK) properties that are better suited for oral/chronic use. Recently presented at the American Epilepsy Society, SAGE has the capacity to modify and switch out chemical groups on the backbone of neurosteroids in a way that retains the $GABA_A$ receptor modulation properties but alters PK. SAGE notes the tremor/PPD Phase II studies are relatively cheap ways to examine the $GABA_A$-R PAM thesis in new indications, while also providing additional safety exposure for '547 which bolsters the database for the SRSE NDA.

EXPLORING THE CLINICAL POTENTIAL OF SAGE'S $GABA_A$-R MODULATION PLATFORM IN PPD

Postpartum Depression (PPD) is characterized by an irritable, severely depressed mood that occurs within 4 weeks of giving birth. According to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV), PPD is not a separate indication, but exists as a part of the spectrum of major depression, coded with a modifier for postpartum onset. DSM-IV stipulates that the onset must be within 4 weeks of delivery of a neonate. The prevalence is of PPD is 10-13%, rendering it one of the most common complications of childbirth. PPD is believed to be triggered by some component of pregnancy, delivery, or the biological/hormonal changes in the postpartum period. While the PPD phenotype is not codified in a distinct manner, specialists

with whom we spoke state that PPD is generally more-treatment resistant, more often requires combination therapy, and is relatively more anhedonic than other types of depression. Even using relatively conservative estimates, PPD represents a relatively large market opportunity. With 3.8MM women giving birth each year and a ~10% incidence rate, both per MEDACorp specialists and SAGE company estimates, there are ~380K PPD patients in the US at a given time. If one were to assume an average of 6 months of treatment at a cost of $2K/mo, this calculates to a ~$1B US revenue opportunity at just 15% penetration.

SAGE's phase IIa study will evaluate a 3-day infusion of SAGE-547 in ~10 patients with serious PPD. In addition to safety, tolerability and pharmacokinetics, patient symptom response will be evaluated on the Hamilton Rating Scale for Depression (HAM-D-17) and individual Clinical Global Impression-Improvement (CGI-I) Scale scores. As the study is small and open-label, SAGE has said previously that it is looking for a relatively strong response. While MEDACorp specialists are generally cautious regarding open-label data in CNS/mood-disorders, they believe that a 30-40% benefit on the HAM-D-17 would be indicative of a drug effect, especially since the primary endpoint is being captured at day 4 whereas anti-depressants usually take ~2 weeks to confer meaningful symptom control. KOLs will also be looking closely at question #3 (suicidality), and believe a significant change on this measure (even if the overall effect size is a ~20% benefit) could also be clinically meaningful. Ultimately, the enrolled patient population will be important to the interpretation of the results, and we'd expect patients in the study to be relatively more serious - HAM-D-17 scores above 19 suggest severe depression, while scores between 8-13 and 14-18 are associated with depression that is mild and moderate.

The potential relevance of allopregnanolone (ALLO) in PPD is supported by both a strong biological rationale as well as a collection of studies that show a tie between PPD, extra-synaptic $GABA_A$-Rs and ALLO levels in clinical/preclinical settings. Allopregnanolone is the active metabolite of progesterone, and is known to increase to concentrations that are >30 fold normal levels during the third trimester. Once childbirth occurs, progesterone levels (and consequently ALLO levels) return to pre-pregnancy baseline. Shown in the table below, many published articles posit that reduced levels of allopregnalalone in the peripheral blood or CNS may be associated with PPD, major depression, anxiety, and potentially even other CNS ailments such as movement disorders and epilepsy. We know from SAGE-547 preclinical and clinical data that ALLO has a profound effect on the GABA system which has been validated for decades as a potential instigator in depression and anxiety. If the ALLO hypothesis in PPD proves to be true, a $GABA_A$ allosteric modulator of synaptic and extra-synaptic receptors (i.e. a follow on, oral formulation of '547) could be used as a therapy to slowly wean a patient off of ALLO from levels that are ~30 fold higher than normal to ~20x, ~10x, ~5x and then baseline.

Various Studies Posit a Connection between ALLO, PPD and GABA

Date	Publication	Authors	Title	Primary Conclusion	Secondary Conclusion
21-May-14	*Psychopharmacology*	Schiller et al.	Allopregnanolone as a mediator of affective switching in reproductive mood disorders	Depression symptoms were negatively correlated with the change in ALLO following progesterone addback in women with a history of PPD vs. control women	
3-May-06	*Psychopharmacology*	Epperson et al.	Preliminary evidence of reduced occipital GABA concentrations in puerperal women: a 1H-MRS study	Cortical GABA and plasma ALLO concentrations were reduced in both groups of postpartum women, regardless of PPD diagnosis, compared to healthy follicular phase women (vs. no correlation between cortical GABA concentrations and estradiol, progesterone, ALLO, or PREG)	Both postpartum groups had significantly lower cortical GABA concentrations than the follicular HC group; for ALLO, follicular HCs have higher ALLO levels than both postpartum health controls
1-Jun-06	*Am J Psychiatry*	M. Bloch et al.	Effects of Gonadal Steroids in Women with a History of Postpartum Depression	Direct evidence in support of the involvement of estrogen and progesterone in the development of PPD; Women with a history of postpartum depression are differentially sensitive to mood-destabilizing effects of gonadal hormones	Adding back supraphysiologic doses of estradiol and progesterone for 8 weeks, and then withdrawing both steroids under double-blind conditions, precipitated PPD during the withdrawal period in 62.5% (n=5/8) of women with a history of PPD (vs. 0% in comparison group)
1-Jan-01	*Obstet Gynecol*	R. Nappi et al.	Serum Allopregnanolone in Women With Postpartum "Blues"	Serum ALLO levels were detectable postpartum and were significantly decreased in women with maternity "blues"	
23-Nov-05	*Psycheoneuroendocrinology*	A.M. Paoletti et al.	Observational study on the stability of the psychological status during normal pregnancy and increased blood levels of neuroactive steroids with GABA-A receptor agonist activity	PREG, ALLO, and THDOC levels were higher during the luteal phase than during the follicular phase and further increased during pregnancy in young healthy women; increase could be indicative of protection against maternal anxiety and stress	
31-Jul-08	*Neuron*	Maguire and Mody	GABA-A R Plasticity during Pregnancy: Relevance to Postpartum Depression	Significant decrease in tonic and phasic inhibitions in pregnant mice, mediated by a downregulation of GABAAR-δ and g2 subunits, respectively, which rebounds immediately postpartum	
12-Jan-12	*Neuron (Review)*	Brickley and Mody	Extrasynaptic $GABA_A$ Receptors: Their Function in the CNS and Implications for Disease	Tonic form of inhibition in thalamus mediated by the δ-$GABA_A$R extrasynaptic GABA-A receptors that may contribute to stress-, ovarian cycle-, and pregnancy-related mood disorders	
28-Feb-07	*The Journal of Neuroscience*	Maguire and Mody	Neurosteroid Synthesis-Mediated Regulation of $GABA_A$ Receptors: Relevance to the Ovarian Cycle and Stress	The correlation between elevated levels of neurosteroids over the ovarian cycle and altered expression of $GABA_A$R subunits, specifically upregulation of $GABA_A$R subunit expression appears to be analogous to the effect of elevated neurosteroid levels after stress.	

ALLO: allopregnanolone
PREG: pregnenolone
THDOC: allotetrahydrodeoxy-corticosterone

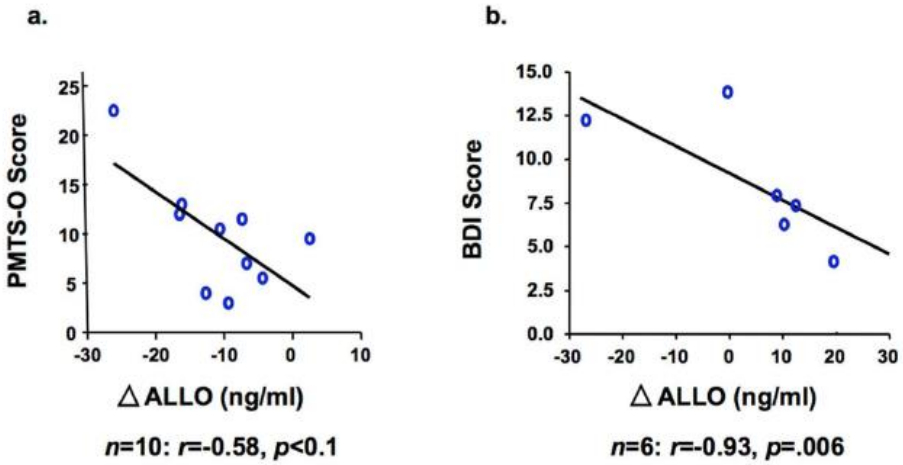
Source: Psychopharmacology, Am J Psychiatry, Obstetrics and Gynecology, Psychoneuroendocrinology, Neuron and the Journal of Neuroscience

Two small studies of Lupron-treated patients with post-menstrual depression and PPD found an association between changes in allopregnanolone levels and measures of tension and depression. Lupron is a depo-GnRH (gonadotropin-releasing hormone) agonist that is often used for the treatment of serious endometriosis and uterine fibroids. Patients treated with Lupron often suffer from anxiety, depression and other problematic symptoms, leading to the generation of endometriosis patient support websites such as "ihatelupron.com". By radically reducing levels of progesterone and estradiol, Lupron can have a deleterious effect on bone mineral density (BMD). This leads physicians to prescribe "add-back" therapy to patients, or small doses of progesterone and estrogen to abate Lupron's impact on BMD. Shown below, in 10 patients, it was found that smaller reductions in allopregnanolone levels after add-back therapy were associated with improvements on the PMTS-O (premenstrual tension scale). Moreover, in a second study of 6 patients treated with Lupron who had a history of PPD, it was found that changes in ALLO pre- and post- add-back therapy were strongly correlated with changes in the

BDI (Beck Depression inventory). Overall, each of these studies is small, retrospective and presents limitations, but taken together fit with the narrative put forth by the ALLO/PPD hypothesis.

Psychopharmacology (2014) – Changing Levels of ALLO Associated with Tension/Depression

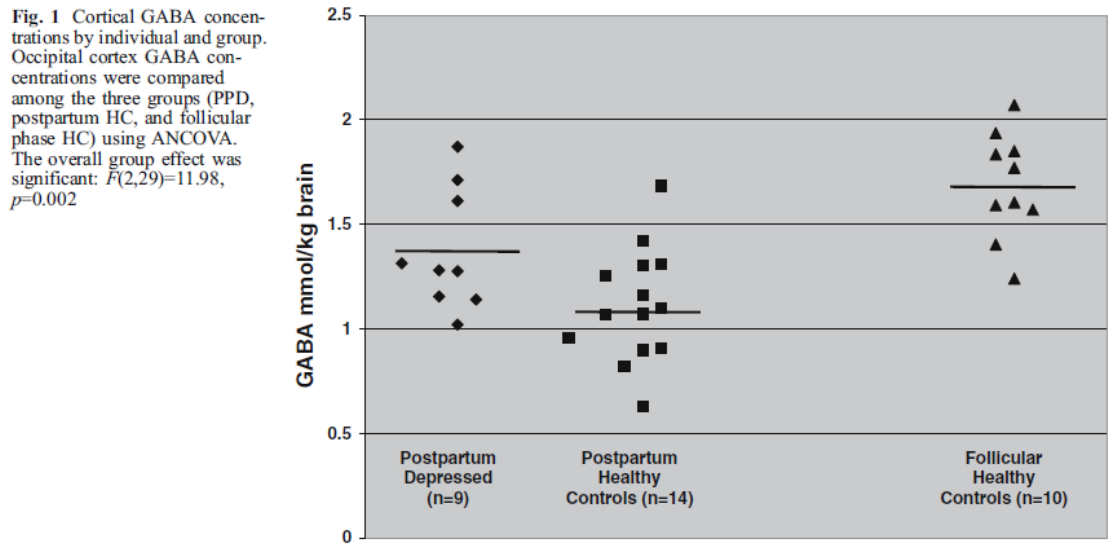
Fig. 1 Correlations between psychiatric symptoms and the change in circulating ALLO concentrations between the second and fourth weeks of progesterone addback in women with a current PMD and b a history of PPD. *PMD* premenstrual dysphoria, *PPD* postpartum depression, *PMTS-O* Premenstrual Tension Scale — Other Rating, *BDI* Beck Depression Inventory, *ALLO* allopregnanolone



Source: Psychopharmacology (2014) – Schiller et al.

Other research has shown that brain GABA levels are meaningfully reduced after childbirth, lending support to the GABA-hypothesis of PPD. In the study below, nine women with PPD, 14 postpartum healthy controls, and ten healthy follicular phase females underwent proton magnetic resonance spectroscopy to assess levels of GABA, allopregnanolone, estradiol and progesterone. Shown below, this study showed reduced levels of GABA and allopregnanolone in postpartum patients relative to healthy controls who did not recently undergo childbirth, but interestingly, no difference in neurotransmitter/hormone levels between patients with PPD and healthy controls. While at first glance this appears to contradict the data above, the authors of the publication speculated that maybe all postpartum patients have lower levels of GABA and ALLO but PPD patients are those who specifically fail to adapt to a new neuroendocrine milieu. Supportive of this hypothesis, the over half the patients who experienced PPD in this study had prior experience with mood disorders and may have had a reduced threshold to depression onset.

Psychopharmacology (2006) Article Shows Lower Levels of GABA in Postpartum Brain

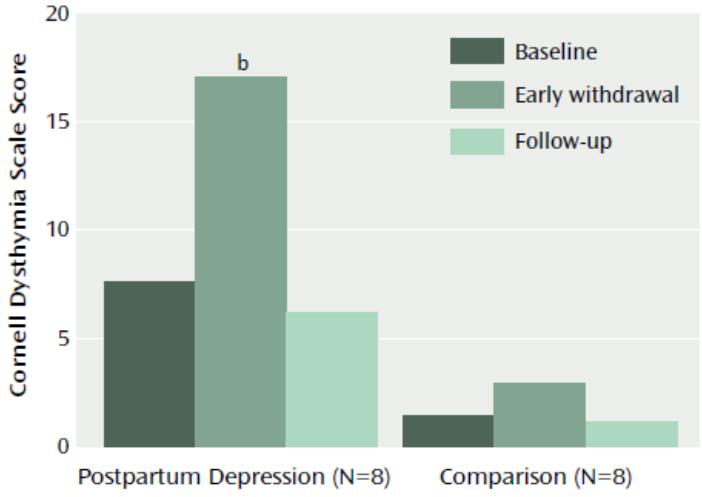


Source: Psychopharmacology, Epperson et al. 2006

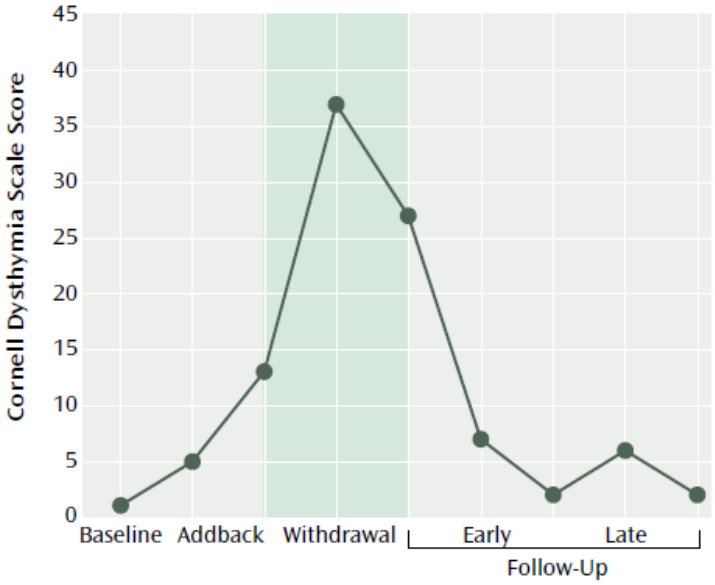
Supportive of the hypothesis put forth above, a study of 16 healthy women (8 who had a history of PPD, 8 who did not) found that those with prior experience with PPD were much more vulnerable to depression during hormonal changes. The supra-physiologic gonadal steroid levels of pregnancy and withdrawal from these high levels to a hypo-gonadal state were stimulated in 16 healthy women, half of whom had a history of PPD. Patients received Lupron (GnRH agonist), then supra-physiologic doses of estradiol/progesterone, then withdrawal of both steroids under double-blind conditions. Interestingly, five of the eight women with a history of PPD (~63%) developed significant mood symptoms during the withdrawal period versus 0 of the 8 patients who had no history of PPD. Moreover, throughout the study, patients with a history of PPD experienced much more mood volatility, and on average showed a doubling from baseline in their Beck Depression Inventory scores. The authors of this study concluded that women with a history of PPD may be differentially sensitive to mood-destabilizing effects of changing levels of gonadal steroids, which we see as supportive of the clinical utility of SAGE-547 treatment.

Am J Psychiatry (2006) Article Shows Significant Mood Changes in Pts with PPD History in Hormonal Simulation of Pregnancy and Childbirth

FIGURE 1. Mean Scores on the Cornell Dysthymia Scale Before and After Estrogen and Progesterone Replacement in Eight Women With a History of Postpartum Depression and Eight Normal Comparison Women[a]



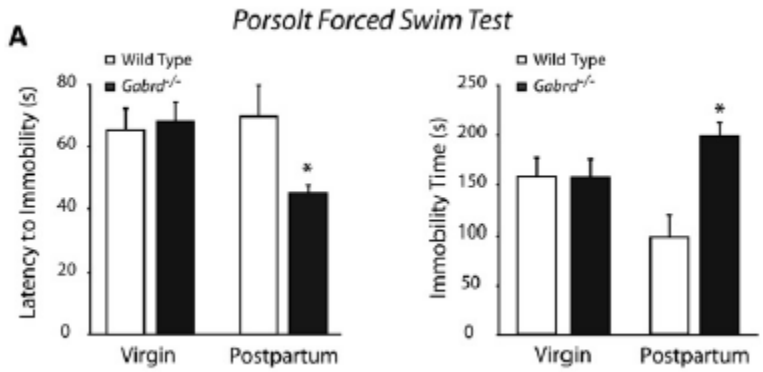
[a] Study phases: 8-week baseline, when no medications were administered; 4-week early withdrawal, when estradiol and progesterone, previously administered during an 8-week addback period, were withdrawn; and 8-week follow-up, when no medications were administered.
[b] Significant difference between baseline and withdrawal periods in the group with a history of postpartum depression (Bonferroni post hoc t test, $p<0.01$).



Source: American Journal of Psychiatry, Bloch et al. (2006)

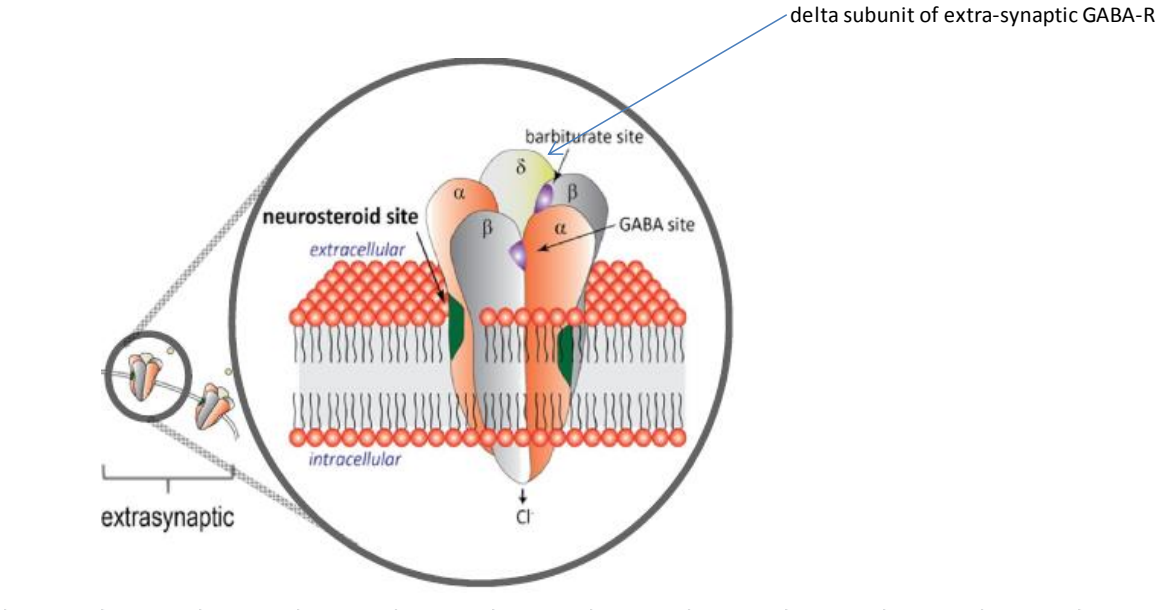
A study in a mouse model of PPD found that the presence of depression after childbirth was associated with mutations in delta- GABA$_A$-R, or the equivalent of extra-synaptic GABA$_A$ receptors. In this study published in *Neuron* (*Maguire et al., 2008)*, the investigators examined the impact of changing hormonal levels in mice which have normal and lack GABA-R delta receptor subunits (Gabard+ or Gabard-), or those relevant to the expression and stability of extra-synaptic receptors (a diagram of extra-synaptic GABA$_A$-Rs is shown below). To determine the behavioral impact of GABA$_A$-R regulation during pregnancy and postpartum, the Porsolt forced swim test (which has been shown to be sensitive to antidepressants) was employed to assess motivation and anhedonia. Shown below, Gabard- mice displayed a decreased latency to immobility and an increase in total immobility time (two markers of depressive behavior) relative to healthy controls in the postpartum period. No difference was observed between the mice pre-childbirth. Most interesting is the fact that the onset of depressive symptoms was *only* shown in the postpartum period, suggesting that delta- GABA$_A$-R (or, extra-synaptic GABA$_A$-R) may be a relevant player in PPD specifically and not necessarily in major depressive disorder.

Neuron (2008) – Mice with Mutated Delta- GABA$_A$-R Subunit Are Relatively More Susceptible to Depression after Childbirth



*Source: Neuron, Maguire et al. (2008), *p<.05*

Diagram of Extra-Synaptic $GABA_A$ Receptor



Source: Company Presentations

Experiments by Maguire and Mody (2007) showed similar effects on extra-synaptic delta-$GABA_A$-Rs in response to both ovarian and stress hormones in the preclinical models. In a series of experiments, investigators showed that acute stress causes an increase in $GABA_A$-R delta subunit expression compared relative to unstressed control mice, suggesting that this receptor system may be protective and adaptive to various conditions. While in preclinical models, we believe this further supports the hypothesis that disruption in the balance between excitation and inhibition after an acute stressful episode may be associated with alterations in extrasynaptic $GABA_A$-Rs, or that extra-synaptic receptors are important for one's ability to adapt to acute changes.

Despite all the evidence supporting the importance of GABA in PPD, however, specialists only use benzodiazepines in post-partum depression patients with co-morbid anxiety and don't consider benzos a PPD monotherapy. This provides some counter-evidence to the studies that stress the importance of GABA above, however it's also possible that solely modulating GABA through synaptic receptors is insufficient on its own to improve mood in PPD.

EXPLORING THE CLINICAL POTENTIAL OF SAGE'S $GABA_A$-R MODULATION PLATFORM IN TREMOR

Essential tremor (ET) is one of the most common movement disorders. Tremor impacts ~10MM patients in the US, ~10-15% of whom are treated with pharmacotherapy, according to MEDACorp specialists and SAGE company estimates. According to a recent review of pharmacotherapy for tremor (published in *CNS Drugs* in 2008 – since, little has changed),

currently available medications are able to effectively confer symptom control in only ~50% of patients ET. ET is common in patients with neurodegenerative disorders such as dementia or Lewy Body's disease. Shown below, ET is differentiated based from Parkinson's disease and dystonia via many features including (1) a lack of arm and leg tremors, (2) a lack of rigidity, (3) a lack of tremor directionality and (4) a lack of pain. Like PPD, ET represents a very large market opportunity: with ~1MM patients on pharmacotherapy in the US, per MEDACorp specialists and SAGE company estimates, a ~$10k/year drug that captures 8% market share would generate almost $1B in sales.

Distinguishing Essential Tremor from Parkinson's Disease and Dystonia

	ET	PD	Dystonia
Action tremor in arms, hands, or head	++	++	++
Hemi-body (arm and leg) tremor	..	++	..
Action tremor > rest tremor	++	+	++
Rest tremor > action tremor	..	++	..
Rigidity or bradykinesia (excluding cogwheeling without rigidity)	..	++	..
Dystonic movements and postures in tremulous body region	..	+	++
Tremor is non-rhythmic	..	..	++
Tremor is directional (amplitude greater in one direction)	..	..	++
Null point (limb or neck position that lessens the tremor)	+	+	++
Sensory trick	..	..	++
Muscle hypertrophy (in neck when neck tremor is present)	..	..	++
Pain (in neck when neck tremor is present)	..	..	++
Pulling sensation	..	..	++

·=Does not occur; +=sometimes occurs; ++=often occurs.

Table 1: **Clinical differentiation of ET, Parkinson's disease (PD), and dystonia**

Source: Lancet Review on Essential Tremor

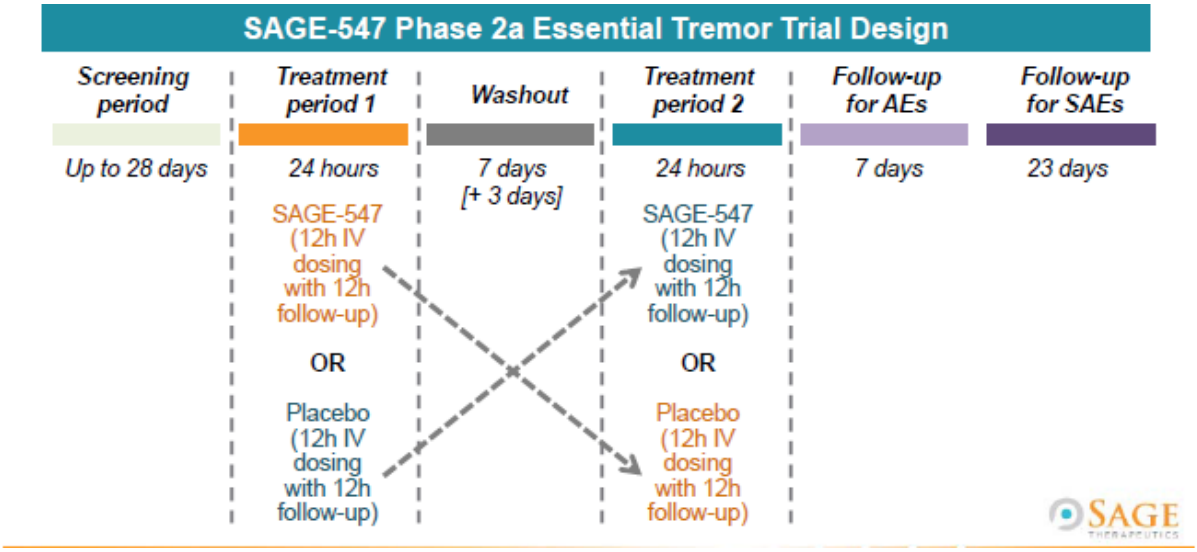
Generally speaking, $GABA_A$-Rs are a validated target for the treatment of essential tremor. On tremor support websites from the Mayo clinic, MedScape, and essentialtremor.org, benzodiazepines such as Kilonipin, Xanax and Ativan, which all modulate synaptic $GABA_A$-R -Rs, are all listed as treatments for ET. Specialists with whom we spoke generally use beta blockers first because of their relatively better tolerability profile, but often switch to or add-on benzos when tremors progress or present as more serious. KOLs state that benzodiazepines will at least be somewhat effective in most ET patients; however the biggest question is whether or not sedative side effects can be managed, or in other words, whether or not the therapeutic window for a given benzo is wide enough for a given patient. Shown in the table below, multiple publications have explored and corroborated the GABA ET hypothesis, and generally suggest that GABAergic neuronal loss as well as lower levels of circulating GABA may be antecedents to or associated with essential tremor. Unlike with PPD, however, we found little in the literature that hypothesizes a potential tie between tremor and extra-synaptic $GABA_A$-Rs specifically.

Various Publications Find Tie between GABA and Pathophysiology of ET

Date	Publication	Authors	Title	Primary Conclusion	Secondary Conclusion
16-Jun-14	*Tremor and Other Hyperkinetic Movements*	Gironell et al.	The GABA Hypothesis in Essential Tremor: Lights and Shadows	Findings from several studies support the GABA hypothesis in ET. The hypothesis follows four steps 1) cerebellar neurodegeneration with Purkinje cell loss; 2) a decrease in GABA system activity in deep cerebellar neurons; 3) disinhibition in output deep cerebellar neurons with pacemaker activity; and 4) an increase in rhythmic activity of the thalamus and thalamocortical circuit, contributing to tremor generation.	The GABA hypothesis continues to be the most robust pathophysiological hypothesis to explain ET.
30-May-12	*Brain*	Epperson et al.	Preliminary evidence of reduced occipital GABA concentrations in puerperal women: a 1H-MRS study	Authors found a post-mortem decrease in GABA-A (35% reduction) and GABA-B (22–31% reduction) receptors in the dentate nucleus of the cerebellum from individuals with essential tremor, compared with controls or individuals with Parkinson's disease, as assessed by receptor-binding autoradiography.	It is proposed that a decrease in GABA receptors in the dentate nucleus results in disinhibition of cerebellar pacemaker output activity, propagating along the cerebello-thalamo-cortical pathways to generate tremors
2-May-14	*Progress in Neurobiology*	Schmouth et al.	Genetics of essential tremor, From phenotype to genes, insights from both humans and mouse studies	Review article on tremor highlights multiple pieces of supporting evidence for the GABA hypothesis including (1) to he dentate nucleus has been demonstrated to have decreased levels of gamma-aminobutyric acid-A (GABA-A), and GABA-B receptors in patients with ET, which correlated with progression of the disease balance by (2) the fact that benzodiazepines are effective in some but not all patients, implying that ET is heterogenous	

Source: Tremor and Other Hyperkinetic Movements, Brain and Progress in Neurobiology

SAGE's phase II Essential Tremor study will enroll ~24 patients, each of whom will receive both drug and placebo in a crossover design. Shown below, the trial is comprised of two 24-hour treatment periods each separated by a 7-day washout. Tremor patients in the active arm will receive a '547 infusion for 12 hours after which the amplitude of patients' tremors will be assessed via a transducer. Specialists note that this method is a fairly straightforward way to assess tremor activity and severity. Additionally, the trial also contains a clinical measure (The Essential Tremor Rating Scale (TETRAS)) on which physicians will assess tremor severity and interference as patients perform various movements.



Source: Company Presentations

MEDACorp specialists believe that any statistically significant impact on the ET study's primary endpoint would be clinically meaningful, as long as SAGE-547's safety profile is also favorable. We find it somewhat challenging to handicap exactly what to expect regarding efficacy/safety in the ET study since based on the inclusion/exclusion criteria, one does not know exactly what types of patients will be enrolled. It's possible that study entrants will be treatment naïve, treatment failures, and/or receiving combo-therapy with SAGE-547 and either a beta blocker or a benzodiazepine. However, as multiple therapies are available for ET, we'd guess that trial enrollment will be biased (as seen in epilepsy and other CNS areas) toward patients who are not-well-controlled on the standard-of-care. Assuming that this is the case, KOLs believe that any statistically significant effect on the primary endpoint and the TETRAS would justify use of SAGE-547 in this indication. If the study hits its efficacy endpoint, of primary importance to physicians will be rates of sedation, and specifically whether these rates are the same, higher or lower than benzodiazepines. Shown below, most benzodiazepines produce problematic sedation in ~15% of patients according to their FDA labels. However specialists estimate that these rates are higher in ET (closer to 50%), which is consistent with warnings on FDA benzodiazepine labels that sedation occurs more often and at lower doses in elderly patients.

Sedation Rates of Benzodiazepines		
FDA Label Sedation Rates May Be Underestimate in ET, as Sedation Rates Increase with Age		
Drug	**N**	**Rate of Sedation on FDA Label**
Ativan	3500	16%
Klonopin	850	14% low dose, 40% high dose
Xanax	1070	15%

Source: FDA Labels

VALUATION

We derive a $93 (from $70 previously) per share price target for SAGE shares based on an 11% discount rate and a 3% terminal growth rate. Our base case assumption assumes ~$1.36B in peak-risk adjusted 2024E sales based on a 70% probability of approval for SAGE-547, and assumes ~$380MM in peak revenues in 2027E for SAGE-689 and SAGE-217.

RISKS TO VALUATION

Risks to our valuation include disappointing clinical data, regulatory setbacks, and commercial shortfalls. Because SAGE has only one product currently being examined in patients, the occurrence of any of these could impact the stock significantly.

ACKNOWLEDGEMENTS:

Tessa Romero of Leerink Partners Equity Research contributed to this report. Her contribution is greatly appreciated.

SAGE P&L ($MM) GAAP	2013	1Q14	2Q14	3Q14	4Q14	2014	1Q15	2Q15E	3Q15E	4Q15E	2015E	2016E	2017E	2018E
SAGE-547	-	-	-	-	-	-	-	-	-	-	-	-	-	44.2
SAGE-689	-	-	-	-	-	-	-	-	-	-	-	-	-	-
SAGE-217	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Tremor	-	-	-	-	-	-	-	-	-	-	-	-	-	-
PPD	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Total Revenue (p/w)	-	**-**	**-**	**-**	**-**	-	**-**	**-**	**-**	**-**	-	**-**	**-**	**44.2**
COGS	-	-	-	-	-	-	-	-	-	-	-	-	-	4.4
R&D	14.4	4.2	4.4	6.6	8.9	24.1	12.9	14.0	15.0	16.0	57.9	75.3	82.8	91.1
SG&A	3.9	1.6	1.8	2.9	3.4	9.7	4.0	4.1	4.1	4.2	16.4	29.5	53.1	39.8
Operating Expenses	18.3	5.8	6.2	9.5	12.4	33.8	16.9	18.1	19.1	20.2	74.3	104.8	135.9	135.3
Operating Income	(18.3)	(5.8)	(6.2)	(9.5)	(12.4)	(33.8)	(16.9)	(18.1)	(19.1)	(20.2)	(74.3)	(104.8)	(135.9)	(91.1)
Interest Income (Expense)	0.0	-	0.0	0.0	0.0	0.0	0.0	-	-	-	0.0	-	-	-
Other Income (expense)	(0.0)	-	(0.0)	(0.0)	(0.0)	(0.0)	0.0	-	-	-	0.0	-	-	-
EBT	(18.3)	(5.8)	(6.2)	(9.5)	(12.4)	(33.8)	(16.9)	(18.1)	(19.1)	(20.2)	(74.3)	(104.8)	(135.9)	(91.1)
Tax	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Net Income (Loss)	**(18.3)**	**(6.1)**	**(7.8)**	**(9.9)**	**(12.4)**	**(36.1)**	**(16.9)**	**(18.1)**	**(19.1)**	**(20.2)**	**(74.3)**	**(104.8)**	**(135.9)**	**(91.1)**
Diluted EPS	**$ (1.92)**	**$ (3.71)**	**$ (4.57)**	**$ (0.50)**	**$ (0.48)**	**$ (1.67)**	**$ (0.66)**	**$ (0.67)**	**$ (0.68)**	**$ (0.71)**	**$ (2.72)**	**$ (3.69)**	**$ (4.55)**	**$ (2.95)**
Basic Shares Outstanding	9.5	1.6	1.7	19.6	25.7	21.6	25.7	27.0	28.3	28.4	27.3	28.4	29.9	30.9
Diluted Shares Oustanding	9.5	1.6	1.7	19.6	25.7	21.6	25.7	27.0	28.3	28.4	27.3	28.4	29.9	30.9

Source: SEC Filings and Leerink Partners Research

SAGE BS & CFS ($MM) GAAP	2013	1Q14	2Q14	3Q14	4Q14	2014	1Q15E	2Q15E	3Q15E	4Q15E	2015E	2016E	2017E	2018E
Net Cash	**8.1**	**55.2**	**49.1**	**136.7**	**127.8**	**127.8**	**113.2**	**225.4**	**207.4**	**188.4**	**188.4**	**91.8**	**119.1**	**40.5**
Cash & Equivalents	8.1	55.2	49.1	136.7	127.8	127.8	113.2	225.4	207.4	188.4	188.4	91.8	119.1	40.5
Debt	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Change in Cash	**5.3**	**47.4**	**(6.1)**	**81.4**	**(8.8)**	**113.8**	**(14.7)**	**112.2**	**(17.9)**	**(19.0)**	**60.6**	**(96.6)**	**27.3**	**(78.6)**
Operating Cash Flow	**(17.5)**	**(5.6)**	**(6.1)**	**(12.6)**	**(8.8)**	**(33.1)**	**(14.7)**	**(17.0)**	**(17.9)**	**(19.0)**	**(68.6)**	**(95.6)**	**(120.7)**	**(75.6)**
Net Income (Loss)	(18.3)	(5.8)	(7.8)	(9.9)	(12.4)	(35.8)	(16.9)	(18.1)	(19.1)	(20.2)	(74.3)	(104.8)	(135.9)	(91.1)
SOE	0.1	0.2	0.4	0.6	0.7	1.8	1.0	1.1	1.1	1.2	4.5	8.4	13.6	13.1
D&A	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.8	1.6	2.4
Other	0.7	0.0	1.3	(3.3)	2.8	0.8	1.2	-	-	-	1.2	-	-	-
Investing Cash Flow	**(0.0)**	**(0.0)**	**(0.0)**	**(0.0)**	**(0.0)**	**(0.0)**	**(0.0)**	**(0.0)**	**(0.0)**	**(0.0)**	**(0.0)**	**(1.0)**	**(2.0)**	**(3.0)**
CapEx	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(1.0)	(2.0)	(3.0)
Other	-	-	-	-	-	-	-	-	-	-	-	-		
Financing Cash flow	**22.8**	**53.0**	**-**	**94.0**	**-**	**147.0**	**-**	**129.2**	**-**	**-**	**129.2**	**-**	**150.0**	**-**
Equity Issuance (Buyback)	22.8	53.0	-	94.0	-	147.0	-	129.2	-	-	129.2	-	150.0	-
Debt Issuance (Retirement)	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Other	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Source: SEC Filings and Leerink Partners Research

SAGE DCF Analysis	2014	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E	TV
Cash Flow From Operations ($MM)	(33)	(69)	(96)	(121)	(76)	79	253	425	549	600	722	655	602	571	448	361	299	
Cash Flow From Investing ($MM)	(0)	(0)	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(9)	(9)	(9)	(9)	(9)	(9)	
Net Borrowing (Repayment) ($MM)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Free Cash Flow ($MM)	(33)	(69)	(97)	(123)	(79)	75	248	419	542	592	713	646	593	562	439	352	290	3735
Discount Periods	-	-	0.75	1.75	2.75	3.75	4.75	5.75	6.75	7.75	8.75	9.75	10.75	11.75	12.75	13.75	14.75	
NPV FCF ($MM)	-	(51)	(89)	(102)	(59)	51	151	230	268	264	286	234	193	165	116	84	62	801

Sum NPV FCF ($MM)	2603
Net Cash 2Q15E	225
Implied SAGE Mkt Cap ($MM)	**$ 2,828**
SAGE Per Share Value	**$ 93.37**

Cost of Equity	11.0%
TG Rate	3.0%
Diluted Shares Oustanding 3Q15E	30.3

Source: Leerink Partners Research

SAGE-547 SRSE Revenue Model	2014	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E
US Status Epelepticus Patients	150,000	151,350	152,712	154,087	155,473	156,873	158,284	159,709	161,146	162,597	164,060	165,537	167,026	168,530	170,046	171,577	173,121
% refractory to benzodiazepines	33%	33%	33%	33%	33%	33%	33%	33%	33%	33%	33%	33%	33%	33%	33%	33%	33%
Second-Line Status Epelepticus Patients	50,000	50,450	50,904	51,362	51,824	52,291	52,761	53,236	53,715	54,199	54,687	55,179	55,675	56,177	56,682	57,192	57,707
% refractory to AEDs	70%	70%	70%	70%	70%	70%	70%	70%	70%	70%	70%	70%	70%	70%	70%	70%	70%
Refractory Status Epelepticus (RSE) Patients	35,000	35,315	35,633	35,954	36,277	36,604	36,933	37,265	37,601	37,939	38,281	38,625	38,973	39,324	39,678	40,035	40,395
% super refractory - 1 failed wean attempt	71%	71%	71%	71%	71%	71%	71%	71%	71%	71%	71%	71%	71%	71%	71%	71%	71%
Super RSE Patients	25,000	25,225	25,452	25,681	25,912	25,779	25,642	25,128	24,978	25,202	25,429	26,238	26,883	27,414	27,865	28,260	28,616
%RSE treated with SAGE-547	0.0%	0.0%	0.0%	0.0%	0.0%	1.0%	2.0%	4.0%	5.0%	5.0%	5.0%	3.5%	2.5%	1.7%	1.2%	0.8%	0.6%
%SRSE treated with SAGE-547	0.0%	0.0%	0.0%	0.0%	3.0%	15.0%	25.0%	40.0%	50.0%	60.0%	70.0%	49.0%	34.3%	24.0%	16.8%	11.8%	8.2%
Patients on SAGE-547	-	-	-	-	777	4,233	7,149	11,542	14,369	17,018	19,715	14,208	10,176	7,256	5,160	3,661	2,594
Annual Cost of Therapy	$65,000	$65,000	$65,000	$65,000	$65,000	$65,000	$65,000	$65,000	$65,000	$65,000	$65,000	$65,000	$65,000	$65,000	$65,000	$65,000	$65,000
US Gross Revenues ($MM)	0	0	0.0	0.0	50.5	275.1	464.7	750.2	934.0	1106.2	1281.4	923.5	661.4	471.7	335.4	238.0	168.6
Approval Probability	70%	70%	70%	70%	70%	70%	70%	70%	70%	70%	70%	70%	70%	70%	70%	70%	70%
US Probability-Weighted Revenues ($MM)	**0**	**0**	**0.0**	**0.0**	**35.4**	**192.6**	**325.3**	**525.1**	**653.8**	**774.3**	**897.0**	**646.5**	**463.0**	**330.2**	**234.8**	**166.6**	**118.0**
ROW as % of US	0%	0%	0%	10%	25%	35%	45%	50%	50%	50%	50%	83%	130%	201%	198%	195%	193%
SAGE-547 ROW Gross Revenues ($MM)	-	-	-	-	13	96	209	375	467	553	641	763	863	949	664	465	325
SAGE-547 ROW p(w) Revenues ($MM)	**0**	**0**	**0**	**0.0**	**8.8**	**67.4**	**146.4**	**262.6**	**326.9**	**387.2**	**464.6**	**534.3**	**603.8**	**664.1**	**464.9**	**325.4**	**227.8**
y/y Growth Rate						762%	217%	179%	124%	118%	20.0%	15.0%	13.0%	10.0%	-30.0%	-30.0%	-30.0%
	-	-	-	-	63.2	371.4	673.8	1,125.3	1,401.0	1,659.3	1,922.2	1,686.8	1,523.9	1,420.4	999.5	702.9	494.0
SAGE-547 WW P(w) Revenues	**0**	**0**	**0**	**0.0**	**44.2**	**260.0**	**471.7**	**787.7**	**980.7**	**1161.5**	**1361.6**	**1180.8**	**1066.7**	**994.3**	**699.6**	**492.0**	**345.8**

Assumptions	
Annual Cost	$65,000
Probability of Approval	70%

Source: Leerink Partners Research

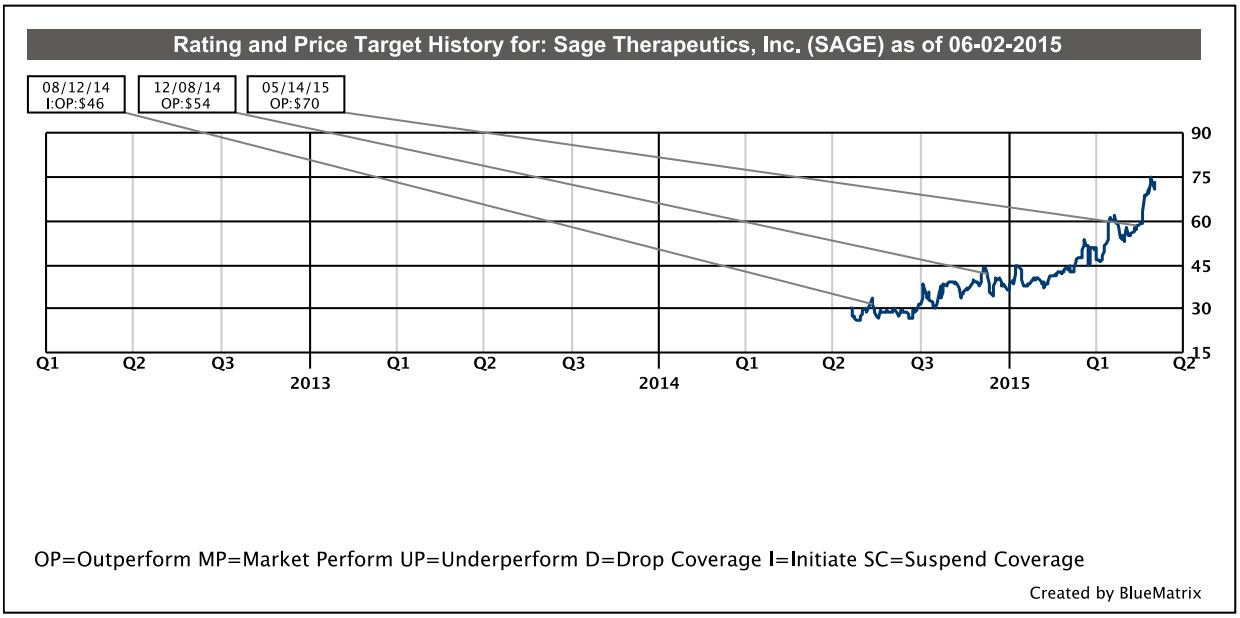
Product	Event	Timing
SAGE-547	Top-line Phase I/II Data	4Q14
SAGE-547	End-of-phase II meeting with FDA	1Q15
SAGE-547	Proof-of-Concept Data for ET and PPD Studies	mid-15
SAGE-547	Initiate Pivotal STATUS Trial	mid-15
SAGE-217	Initiate Phase I Studies	4Q15
SAGE-689	Initiate Phase I Studies	4Q15

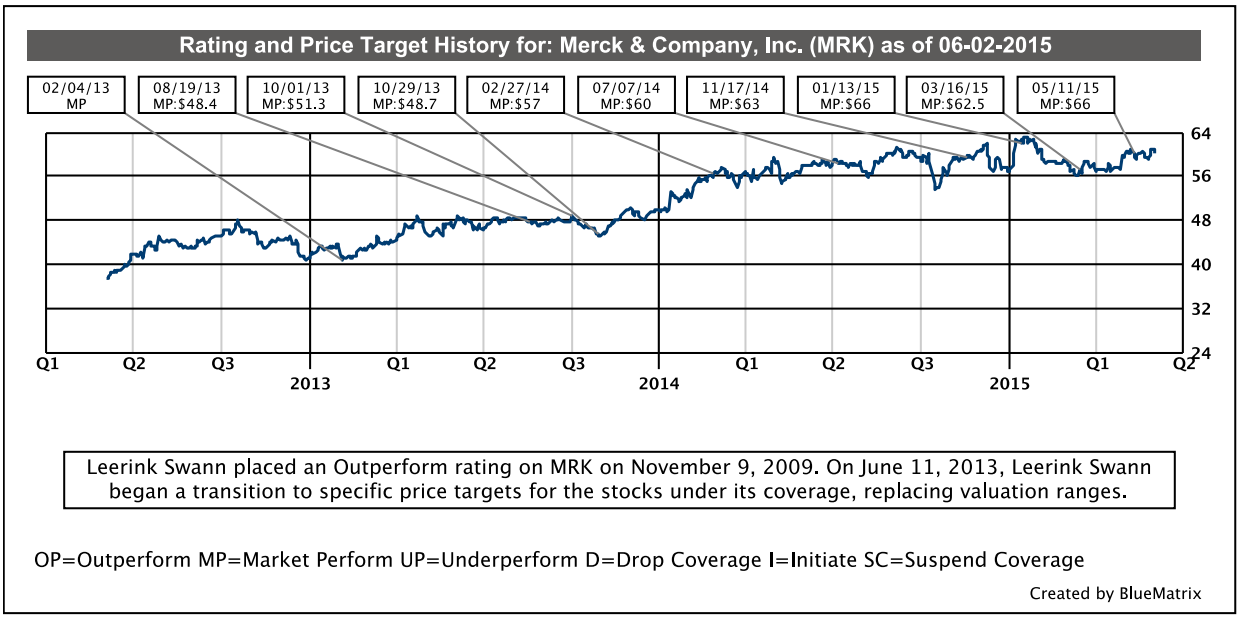
Source: SEC Filings and Leerink Partners Research

Disclosures Appendix

Analyst Certification

I, Paul Matteis, certify that the views expressed in this report accurately reflect my views and that no part of my compensation was, is, or will be directly related to the specific recommendation or views contained in this report.





Distribution of Ratings/Investment Banking Services (IB) as of 03/31/15				
			IB Serv./Past 12 Mos.	
Rating	Count	Percent	Count	Percent
BUY [OP]	151	70.20	55	36.00
HOLD [MP]	64	29.80	2	3.00
SELL [UP]	0	0.00	0	0.00

Explanation of Ratings

Outperform (Buy): We expect this stock to outperform its benchmark over the next 12 months.

Market Perform (Hold/Neutral): We expect this stock to perform in line with its benchmark over the next 12 months.

Underperform (Sell): We expect this stock to underperform its benchmark over the next 12 months.The degree of outperformance or underperformance required to warrant an Outperform or an Underperform rating should be commensurate with the risk profile of the company.

For the purposes of these definitions the relevant benchmark will be the S&P 600® Health Care Index for issuers with a market capitalization of less than $2 billion and the S&P 500® Health Care Index for issuers with a market capitalization over $2 billion.

Important Disclosures

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Leerink Partners LLC makes a market in Sage Therapeutics, Inc.

Leerink Partners LLC is willing to sell to, or buy from, clients the common stock of Merck & Company, Inc. on a principal basis.

Leerink Partners LLC has acted as the manager for a public offering of Sage Therapeutics, Inc. in the past 12 months.

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