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Sage Therapeutics, Inc. and Zogenix, Inc.

AEDD XIII Conference Highlights SAGE-547 Phase I/II Full Data Set and Upcoming Clinical Trials

Sage Therapeutics, Inc.

SAGE (NASDAQ)	$58.44
Stock Rating:	**Outperform**
Company Profile:	**Aggressive Growth**
Price Target:	$75.00

Zogenix, Inc.

ZGNX (NASDAQ)	$1.40
Stock Rating:	**Market Perform**
Company Profile:	**Aggressive Growth**

- We attended the Anti-epileptic Drug and Device Trials (AEDD) XIII Conference in Miami, Florida. The highlight from our coverage was the complete data set presentation of Sage Therapeutics' Phase I/II trial with SAGE-547 in patients with super-refractory status epilepticus (SRSE). In addition, Zogenix presented its Phase III study design and rationale for its product ZX008 to treat Dravet syndrome as it continues the transition from a commercial company focused on chronic pain therapies back to a development-stage company focused on CNS-disorders.

- Sage announced top-line results of its Phase I/II study in conjunction with earnings on May 14. At the conference, Sage Chief Medical Officer Steve Kanes provided additional details including baseline patient characteristics, etiology of disease, subgroup analyses, and the overall safety profile of SAGE-547. In exhibit 1, we show the baseline characteristics of the SRSE patients before SAGE-547 intervention. A mean of 2.1 patient weans were attempted with means of 2.6 anti-epileptics, 1.4 third-line agents (13 patients receiving midazolam, 4 patients receiving pentobarbital, 11 patients receiving propofol, and 2 patients receiving adjunctive ketamine the other third-line agents), and 13.2 concurrent meds. Exhibit 2 shows no differences in efficacy in a subgroup analysis by age, gender, and race with all groups having efficacy in the 70% range, consistent with the overall results. Given that SAGE-547 was administered as an adjunctive therapy, we continue to believe that SAGE-547 is providing a significant clinical benefit to SRSE patients who have not successfully been weaned off of a cocktail of other seizure therapies.

- In a review by Shorvon and Ferlisi in the journal *Brain* in 2012, the authors state that "all anaesthetic drugs, if used in high enough doses, will result in a depth of anesthesia sufficient to abolish seizure activity" and that failure usually occurs due to a dose-limiting adverse effect profile with benzodiazepenes and anti-epileptics. In exhibit 3, we show the safety profile and etiology of diseases in the Phase I/II trial. Overall, the safety profile that includes both the lower and higher doses of SAGE-547 does not show enhancement of the most common dose-limiting adverse effects of midazolam, propofol, and pentobarbital, which include hypotension and cardiac and respiratory depression (Buchhalter *J Epilepsy Curr* 2013). Therefore, we believe that SAGE-547 offers a compelling risk/reward profile for patients with SRSE over the current standard-of-care.

- Following a recent FDA meeting, Sage will initiate its pivotal Phase III trial (STATUS) in the near term, which will be a randomized 1:1 (treatment:placebo in addition to third-line anti-seizure agents), double-blind, placebo-controlled trial designed to assess efficacy and safety in roughly 126 patients (designed to provide the study with 90% power) with SRSE aged 2 years and older. The primary endpoint is successful resolution of status epilepticus (SE) after weaning patient off all third-line agents and SAGE-547 or placebo, without recurrence of SE within 24 hours after completion of a six-day treatment. Secondary endpoints include rate of recovery, regaining of consciousness, mental status, and functional outcome. Last month, Sage also announced the initiation of enrollment in Study 302, its expanded access protocol that provides non-STATUS trial sites access to SAGE-547 in emergency use-cases using the same treatment protocol. These studies, if positive for efficacy, safety, and tolerability, should support an NDA submission in 2017.

- Zogenix's chief medical officer, Dr. Brad Galer, presented an overview of ZX008 (fenfluramine) for the treatment of Dravet syndrome, a disease that results in severe epileptic seizures in children starting in their first year of life that is associated with neurodevelopmental impairment. Dr. Galer spoke to the history with fenfluramine, which is most commonly associated with a withdrawal from worldwide markets due to mitral valve thickening, or valvulopathy, after it was approved for the treatment of obesity in a combination product along with phentermine. Fenfluramine has been examined in an ongoing longitudinal open-label study in Belgium that has seen patients seizure-free for an average of 6 years, with an average treatment length of over 12 years, and no significant cardiotoxicity in the patient population. Zogenix plans to initiate two Phase III trials for ZX008 in the second half of the year that will enroll 55-60 patients per study in a 4-week baseline period, then a titration period for 4-12 weeks that will increase from 2.5 mg BID to 5 mg BID to 10 mg BID if seizure frequency reduction is less than 75% at the higher doses, and a maintenance period of 12 weeks with regular EKG and Doppler monitoring. Patients will then have the option to opt into a one-year open-label safety study to monitor cardiovascular outcomes with the goal of establishing a REMS program if the trials are successful. While we find the ZX008 asset intriguing, we believe that there is significant competition in Dravet syndrome therapies and with a limited patient population, we will be interested to see how the other therapies fare as well and if enrollment goals are maintained in Zogenix's Phase III program.

- **Stock Thoughts.** We continue to believe that Sage Therapeutics is developing an adjunctive therapy to treat patients with a severe unmet medical need. We believe the Phase I/II results show impressive efficacy in a refractory patient population while not significantly affecting the adverse event profile of concomitant therapies. We will wait to see the results of the company's exploratory studies in essential tremor and severe postpartum depression before assigning values to those programs; however, we remain intrigued by pipeline compounds SAGE-217 and SAGE-689 that have shown interesting preclinical data and have the potential to transform Sage into a platform company. We also believe the company's focus on orphan epilepsy therapies may differ from its competitors who have chosen to focus on individual disorders. As Zogenix switches focus from pain therapies to CNS disorders, we remain on the sidelines as we are uncertain of the company's competitive positioning within Dravet syndrome; however, we like the company's strategic refocus on small patient populations with great unmet medical need.

Exhibit 1
SAGE-547 Phase I/II Patient Baseline Characteristics

Characteristic	Mean (Range)	
Male, n	16	
Female, n	9	
Age	48y	(10-76)
Duration of SE	9d	(3-20)
Baseline STESS	3.4	(1-5)
Prior weans	2.1	(0-8)
Antiepileptics	2.6	(0-6)
Third-line agents	1.4	(1-2)
Concurrent meds	13.2	(2-27)
% intubated	100	

Source: AEDDXIII

Exhibit 2
Subgroup Analyses of Responder Group

Subgroup		n/N	%
Gender	Male	10/13	77%
	Female	7/9	78%
Age	≤20 years	2/3	66%
	>20 years	15/19	79%
Race	African American	4/5	80%
	Caucasian	13/17	76%

Source: AEDDXIII

Exhibit 3
Etiology of Disease for Patients in Phase I/II

Etiology	N
Infection	6
Hemorrhage	4
Worsening seizures	3
Unknown	3
Primary or secondary brain tumor	2
Toxic ingestion	2
Anti-NMDA Encephalitis	1
Lupus	1
PRES	1
Sickle Cell Anemia	1
Stroke	1

Source: AEDDXIII

Exhibit 4
Safety Profile of SAGE-547 in Phase I/II Trial

Adverse Events (over 10%)	N	%
Pyrexia	5	20%
Anaemia	4	16%
Blood urea increased	4	16%
Diarrhea	4	16%
Hypotension	4	16%
Convulsion	3	12%
Decubitus ulcer	3	12%
Deep vein thrombosis	3	12%
Haematuria	3	12%
Hypertension	3	12%
Metabolic acidosis	3	12%
Pneumonia	3	12%
Respiratory failure	3	12%
Sepsis	3	12%
Sinus tachycardia	3	12%
Urinary tract infection	3	12%

Serious Adverse Events (over 5%)	N	%
Respiratory Failure	3	12%
Convulsion	2	8%
Pulmonary embolism	2	8%
Renal failure acute	2	8%
Sepsis	2	8%

Cause of Deaths*	N
Cardiopulmonary arrest	3
Organophosphate toxicity	1
Metastatic breast cancer	1
Multiorgan failure	1

*None assessed as drug related

Source: AEDDXIII

Sage Therapeutics Valuation
We rate Sage Therapeutics shares Outperform with a price target of $75. Our price target is based on an NPV analysis of SAGE-547, risk-adjusted 80% for clinical probability of success. We estimate peak sales of SAGE-547 of $1.5 billion by penetrating 65% of the population with SRSE in the United States and 40% of the population in Europe. We do not assign any NPV for the company's pipeline compounds, SAGE-217 and SAGE-689, which would provide upside to our valuation.

Zogenix Valuation
We rate shares of Zogenix Market Perform. We view the company as in the midst of a significant strategic shift from developing and marketing Zohydro to selling the franchise and becoming a CNS drug development company. The company has two primary assets, Brabafen/ZX008, to begin its Phase III clinical program in 2015 with readouts in 2016, and Relday, which will complete its Phase II trial in the second half of 2015 and potentially begin Phase III development in 2016.

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

Zogenix Risks
Key risks to an investment in Zogenix involve clinical risk for the company's pipeline products Relday and Brabafen/ZX008, which are under development for the treatment of schizophrenia and Dravet syndrome, respectively. With the company's recent strategic shift, we also consider the company's ability to develop and commercialize CNS products a risk to investment in shares.

In addition, both companies face competitive risks to their pipeline products for orphan epilepsies.

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Additional information is available upon request.

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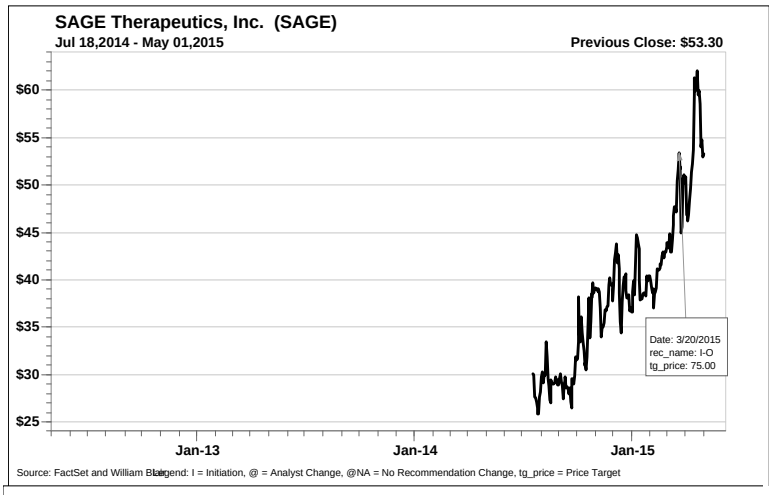
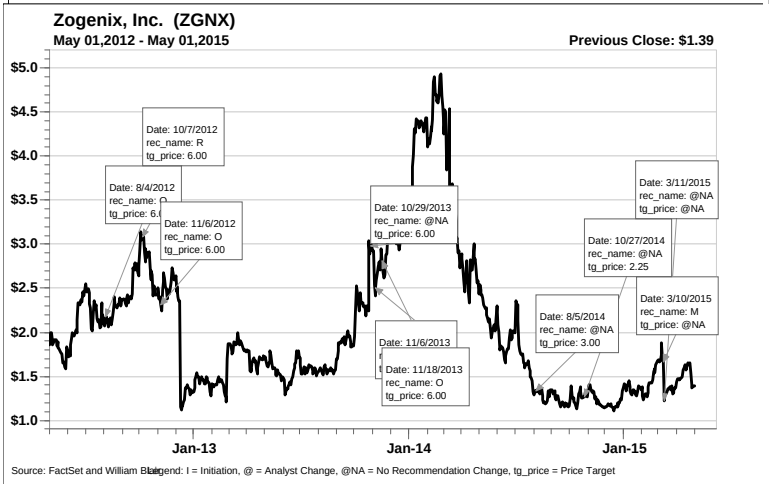
DOW JONES: 18,272.56
S&P 500: 2,122.73
NASDAQ: 5,048.29





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Outperform (Buy)	65	Outperform (Buy)	14
Market Perform (Hold)	32	Market Perform (Hold)	2
Underperform (Sell)	2	Underperform (Sell)	0

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