SAGE THERAPEUTICS

DISCOVER
DEVELOP
DELIVER

Novel Medicines for Life-Altering CNS Disorders

November 2015

Forward-Looking Statements

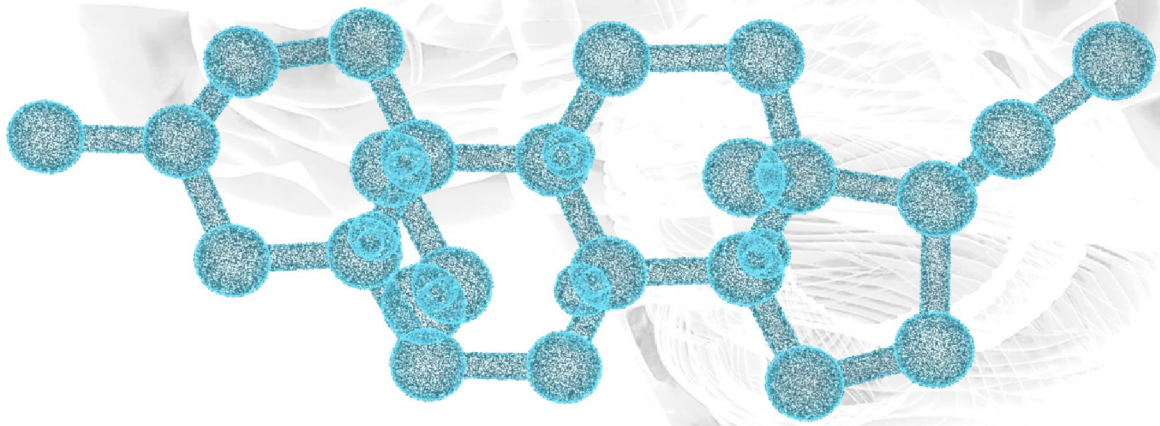
These slides and the accompanying oral presentation contain forward-looking statements, which may be identified by the use of words such as “may,” “might,” “will,” “should,” “expect,” “plan,” “anticipate,” “believe,” “estimate,” “project,” “intend,” “future,” “potential,” or “continue,” and other similar expressions. Forward-looking statements in this presentation include statements regarding: the potential safety, pharmacological effect and efficacy of SAGE’s product candidates; the expected development pathway, anticipated development milestones and possible results in the development of SAGE’s product candidates; the estimated number of cases of SRSE each year and the prevalence of certain other indications for which SAGE may develop its product candidates; expectations regarding commercialization of SAGE-547 in SRSE, if successfully developed; the anticipated impact of SAGE’s development model on future development results and on its ability to advance its pipeline; potential future indications for SAGE’s product candidates; and SAGE’s expectations with respect to cash needs. These forward-looking statements are neither promises nor guarantees of future performance, and are subject to a variety of risks and uncertainties, many of which are beyond SAGE’s control, which could cause actual results to differ materially from those contemplated in these forward-looking statements, including the risk that:

- SAGE may not be able to successfully demonstrate the efficacy and safety of its product candidates at each stage of development;
- success in SAGE’s pre-clinical studies or in earlier stage clinical trials may not be repeated or observed in ongoing or future trials involving the same compound or other product candidates, and future pre-clinical and clinical results for SAGE’s product candidates may not support further development of the product candidate or regulatory approval;
- unexpected safety issues may arise in clinical trials or as a result of non-clinical study data;
- decisions or actions of regulatory agencies may affect the initiation, timing and progress of clinical trials, or may cause us to stop development of a product candidate or may affect SAGE’s ability to obtain marketing approval for its product candidates;
- even if SAGE’s products are successfully developed and approved, the actual market for such products may be smaller than SAGE’s current estimates;
- SAGE’s operating expenses may be higher than forecasted, including if SAGE elects to alter, expand or accelerate its development plans or encounters additional data needs or other hurdles in the course of its activities, and SAGE may also face unexpected expenditures, in either case which may result in the need for additional funding to support its business activities earlier than anticipated;
- Funding to support operations may not be available, when needed, on reasonable terms or at all, or may result in significant dilution to existing shareholders;
- SAGE may not be able to establish and maintain key business relationships with third parties on whom SAGE is, or will need to be, dependent for development or manufacture of products or for future marketing, sales and distribution of products, if SAGE is successful in its development efforts;
- SAGE may not be able to obtain and maintain adequate intellectual property protection or other forms of data and marketing exclusivity for its products, or to defend its patent portfolio against challenges from third parties;
- SAGE may face competition from others developing products for similar uses as those for which SAGE’s products are being developed;
- SAGE may encounter technical and other unexpected hurdles in the manufacture and development of its products.

For additional disclosure regarding these and other risks SAGE faces, see the disclosure contained in the "Risk Factors" section of SAGE’s Quarterly Report on Form 10-Q filed on November 6, 2015, and in SAGE’s other public filings with the Securities and Exchange Commission, available on the SEC's website at http://www.sec.gov. Any forward-looking statement represent SAGE's views only as of today, and should not be relied upon as representing its views as of any subsequent date. SAGE undertakes no obligation to update or revise the information contained in this presentation, whether as a result of new information, future events or circumstances or otherwise.

Innovating Medicines for Life-Altering CNS Disorders

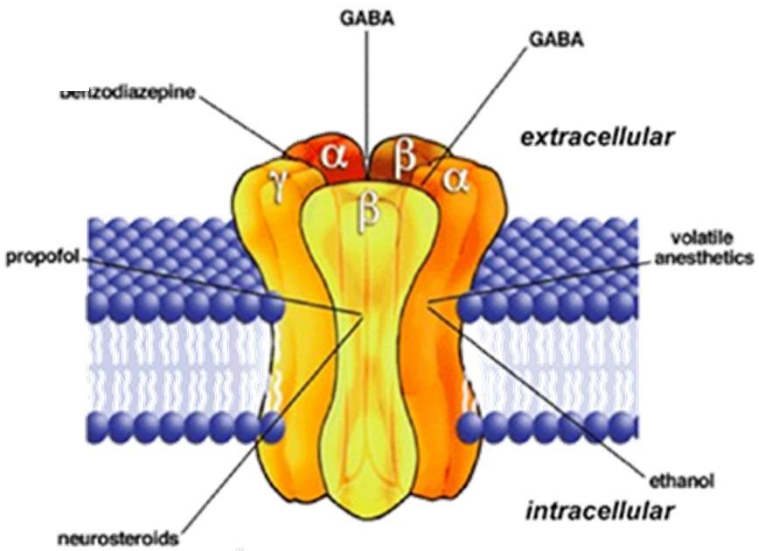
Our mission is to make life better for patients with CNS disorders by DISCOVERING, DEVELOPING and DELIVERING important new medicines for patients in need



Large Portfolio of NCEs Targeting Well-Validated Mechanisms to Control Brain and CNS Function

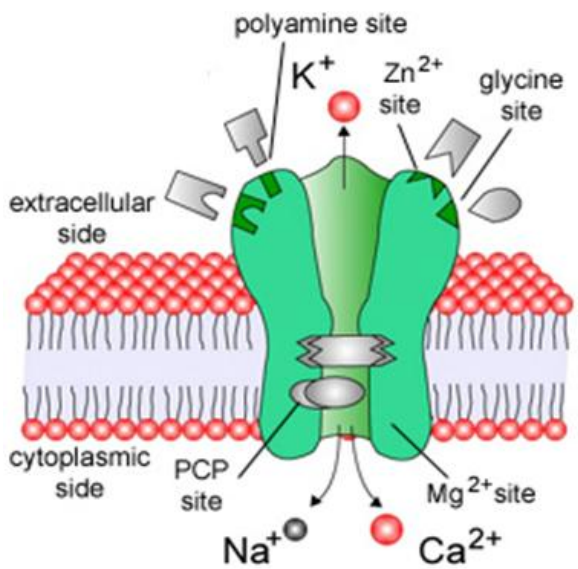
$GABA_A$ Receptors

(inhibiting brain cell firing)



NMDA Receptors

(causing brain cell firing)



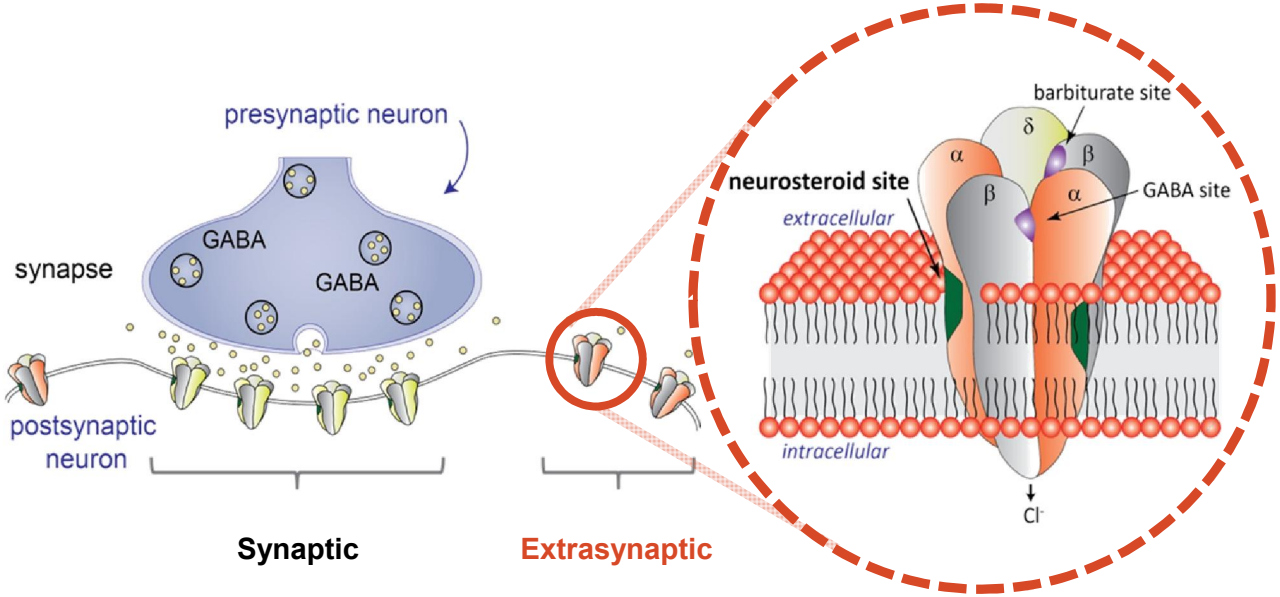
Modulating function of major neurotransmitter systems holds potential for treatment of substantial CNS disease burden

Building a Wholly-Owned Multi-Product CNS Portfolio

	Discovery	Development Candidates	IND Enabling	Phase 1	Phase 2	Phase 3
$GABA_A$ Dysfunction-Related Disorders						
Super-Refractory Status Epilepticus	SAGE-547					
Postpartum Depression	Proof-of-Concept with SAGE-547					
Essential Tremor	Proof-of-Concept with SAGE-547					
	SAGE-217					
High Frequency Seizures in Orphan Epilepsies	SAGE-217					
Status Epilepticus	SAGE-689					
Undisclosed Indications	SAGE-105					
Undisclosed Indications	SAGE-324					
NMDA Dysfunction-Related Disorders						
Smith-Lemli-Opitz Syndrome	SAGE-718					
Anti-NMDA Receptor Encephalitis	SAGE-718					
New Chemical Entities/Undisclosed Indications						

SAGE-547 for Super-Refractory Status Epilepticus

SAGE-547: Novel $GABA_A$ Receptor Modulator



- Synaptic and extrasynaptic allosteric modulator
- Foundational molecule validating $GABA_A$ modulator mechanism of action
- Granted orphan drug for status epilepticus, including SRSE, and Fast Track designation in U.S.
- FDA agreement on SPA for Phase 3 trial in SRSE

SRSE: Rare and Life-Threatening Seizure Disorder with No Approved Treatment

Super-Refractory Status Epilepticus (SRSE)

- Rare, life-threatening condition with high morbidity and mortality rates
- Severe form of status epilepticus that continues for >24 hours despite multiple therapeutic interventions

25,000
Estimated annual SRSE cases in U.S.

>60%
Patients die or remain severely disabled

0
Approved treatments

Sources: DeLorenzo et al. *J Clin Neuro* 1995; 12(4): 316-325.
Claassen et al. *Epilepsia* 2002; 43(2): 146-153.
Novy et al. *Epilepsia* 2010; 51(2): 251-256.

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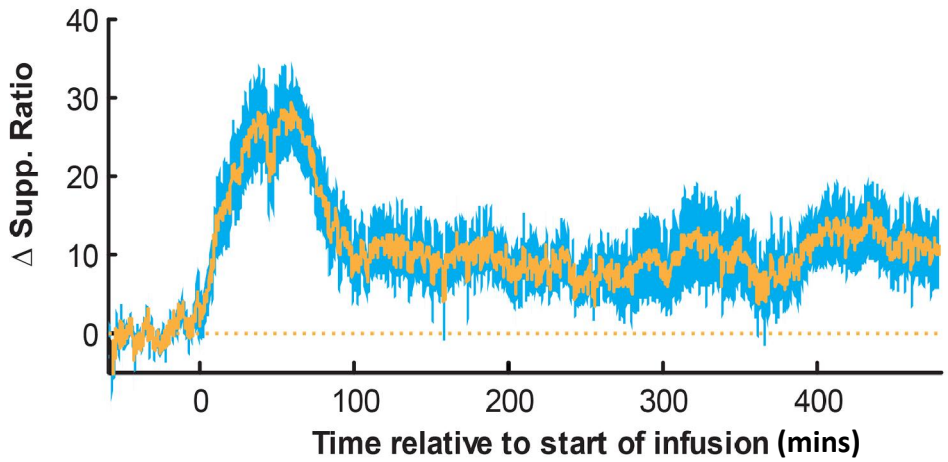
Robust Activity Observed in Phase 1/2 SRSE Trial

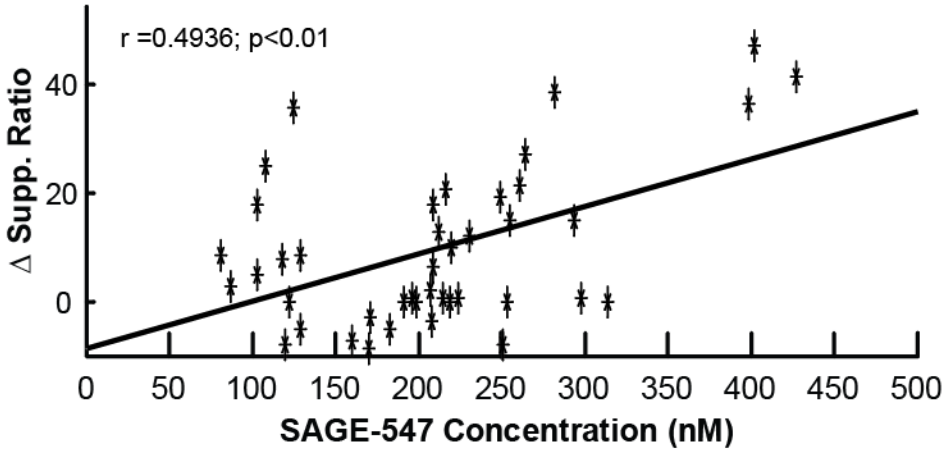
Efficacy Endpoints (n=22 evaluable)

Overall Response Rate	**77% (17/22)**
Standard Dose Response Rate	**81% (13/16)**
High Dose Response Rate	**67% (4/6)**

Significant EEG Suppression (n=14)



Correlation between Dose and EEG Suppression



SAGE-547 Well-Tolerated in Phase 1/2 Trial

- Demonstrated favorable tolerability and positive activity profile
- No serious adverse events deemed drug-related
- Patient deaths due to underlying medical conditions

Serious Adverse Events* (>8%)	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

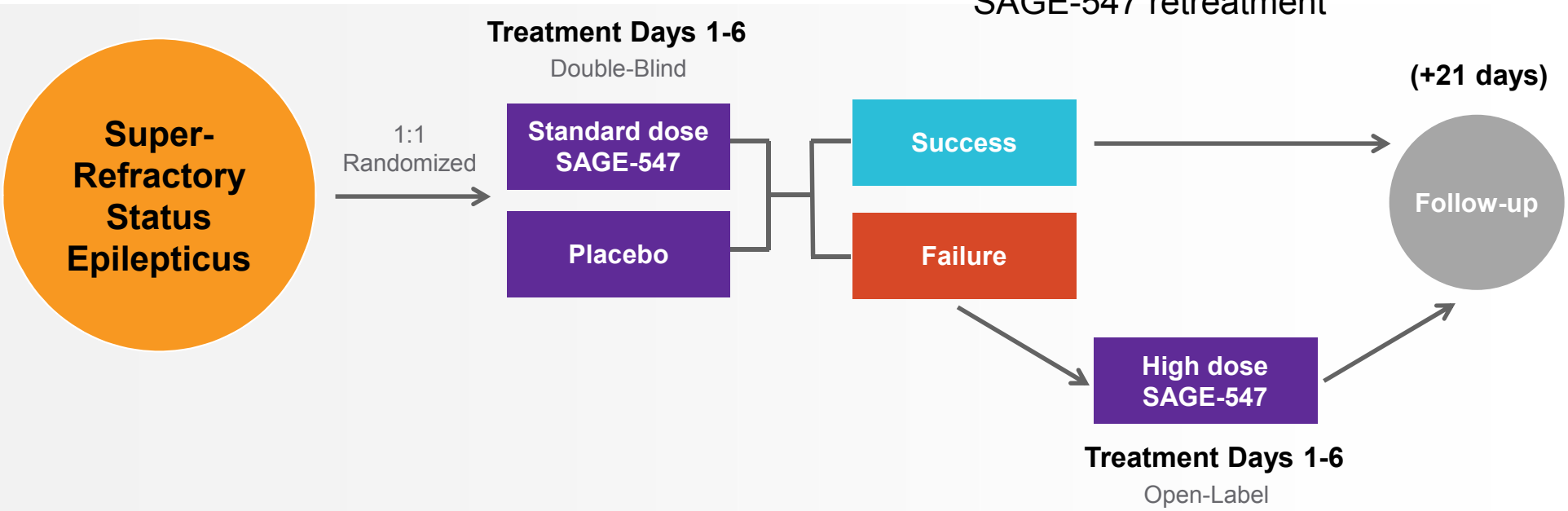
** None assessed as drug-related by Sponsor*

Enrollment is on Track in Phase 3 STATUS Trial of SAGE-547 in SRSE

STATUS TRIAL

Randomized, double-blind, placebo-controlled Phase 3 trial

- **1° Endpoint: Continued resolution of SE for 24 hours following wean of all 3rd-line agents and SAGE-547/placebo**
- SPA agreement with FDA
- 126 evaluable SRSE patients, aged ≥2 years
- ~150 sites in U.S., Canada and Europe
- Non-responders eligible for open-label, SAGE-547 retreatment



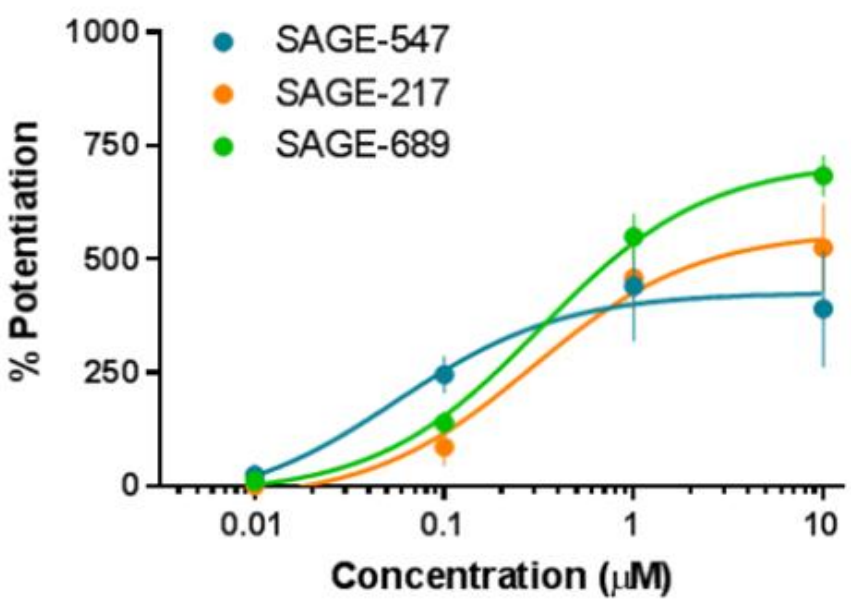
Next Generation GABA Pipeline

SAGE-217: A Chronic Oral $GABA_A$ Modulator in Phase 1 Development

- Differentiated approach through a well-validated mechanism
- Highly potent and selective activity at $GABA_A$ receptors in animal models
- Designed with optimized PK/PD profile intended for once-daily dosing

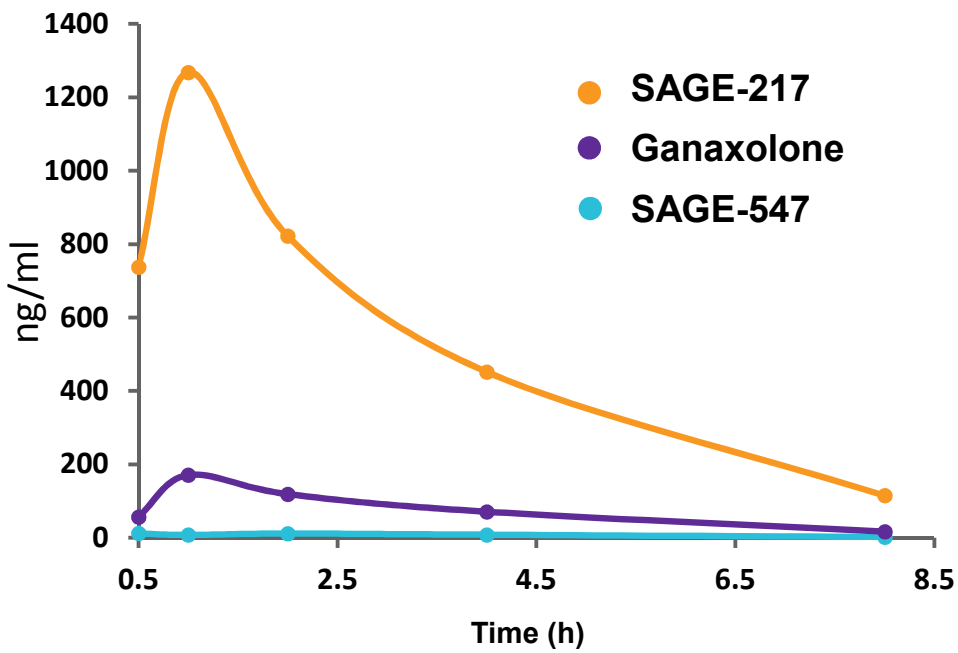
Enhanced Activity at $GABA_A$ Receptors

Activity at Extrasynaptic $GABA_A$ Receptor



Optimized Profile for Oral Use

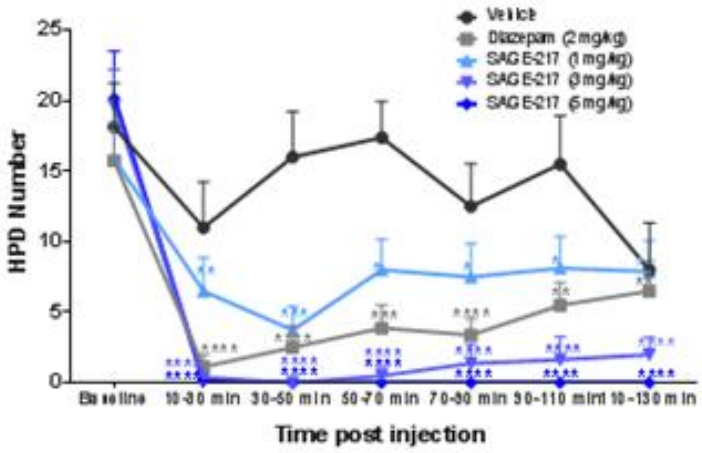
Oral Bioavailability Over Time



SAGE-217 and Related Tool Compounds Have Shown Efficacy Across Numerous Preclinical Models of Seizure

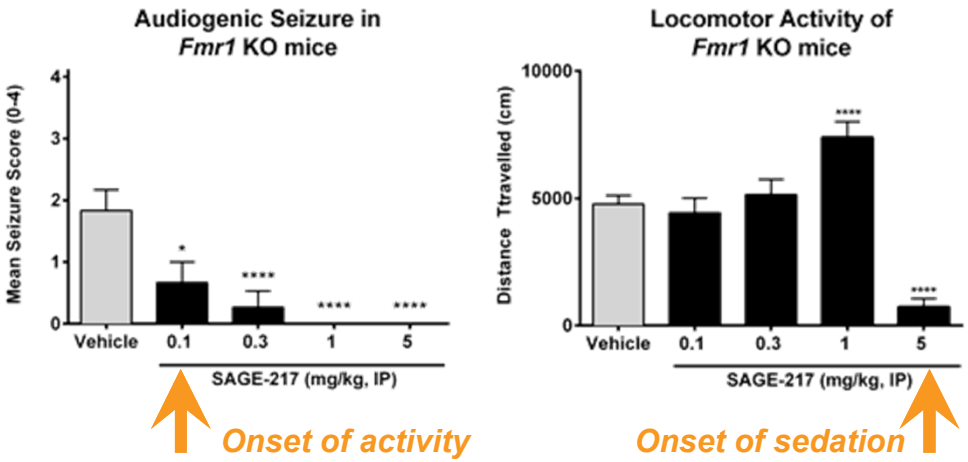
Seizure Suppression in Chronic Epilepsy Model

Rat model of mesial temporal lobe epilepsy



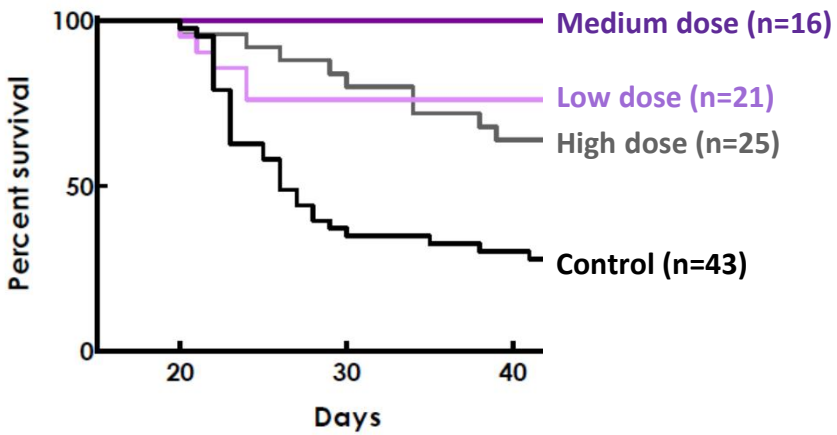
Activity in Genetic Epilepsy Model

Model of audiogenic seizures in Fmr1 knockout mice



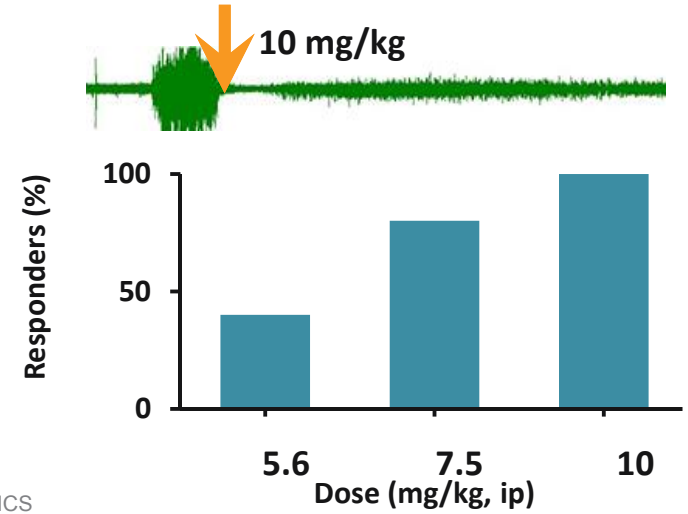
Increased Survival in Genetic Epilepsy Model

Tool compound in model of Dravet syndrome (Scn1a+/- mice)



Acute Suppression of Soman-Induced SE

Tool compound administered 20 mins post-soman treatment



High Frequency Seizure Burden is Significant Across Orphan Epilepsies

Prevalence of Seizures Across Indications

Generalized Seizures	Seizure Type	Lennox-Gastaut	PCDH19	Tuberous Sclerosis	Dravet	Rett
	Tonic-clonic	High	High	High	High	High
	Atonic	High	Moderate	Low	Low	Low
	Partial	Moderate	High	High	High	High
	Tonic	High	Low	Moderate	High	Moderate
	Myoclonic	High	Low	Low	Moderate	Low
	Absence	High	Low	Low	Moderate	Low

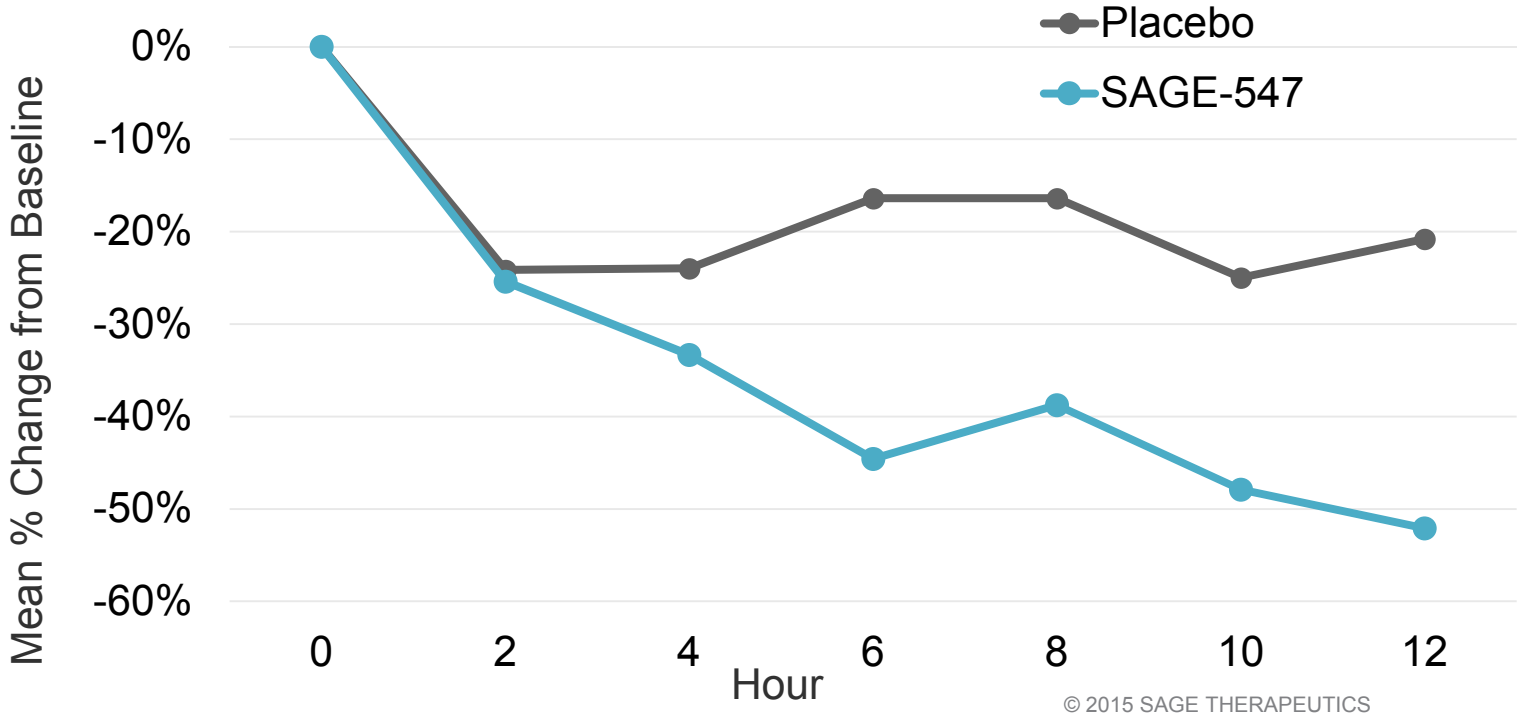
Seizure Burden: High Moderate Low

Source: Data on file

Essential Tremor Proof-of-Concept: Clinically Meaningful Reduction Shown in Tremor Amplitude

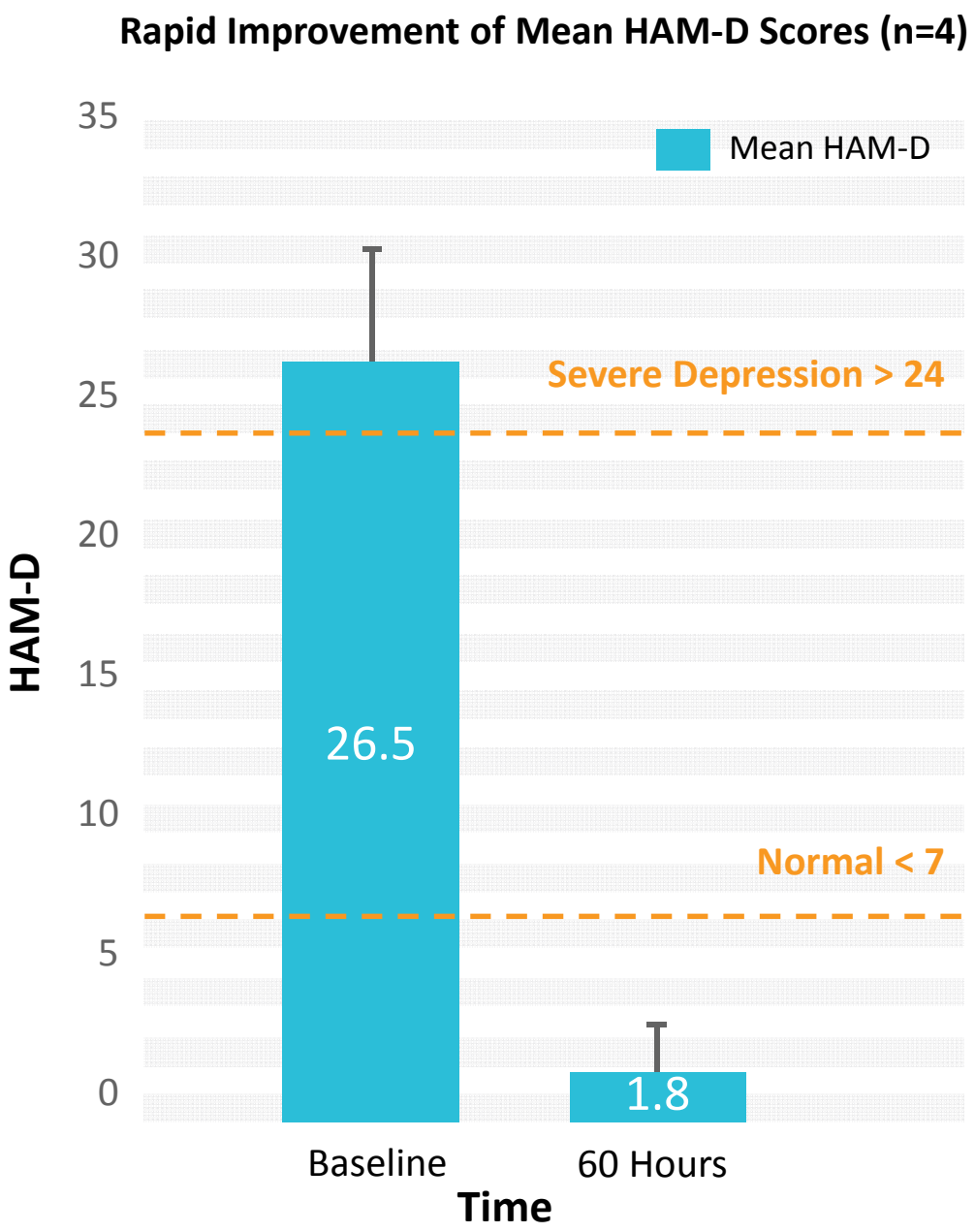
- Pretreated patients (19/25) exposed to target dose for only 2 hours
- SAGE-547 well-tolerated in conscious patients
  - Most common AEs were dizziness and fatigue (during higher dose phase)
  - One patient in higher dose phase discontinued due to hypotension
- Planning to study SAGE-217 in a Phase 2 trial in 2016

Accelerometer Kinetic Tremor Combined Score over Time (p=0.046 at 12 hours)
(Placebo-controlled patients, n=25)



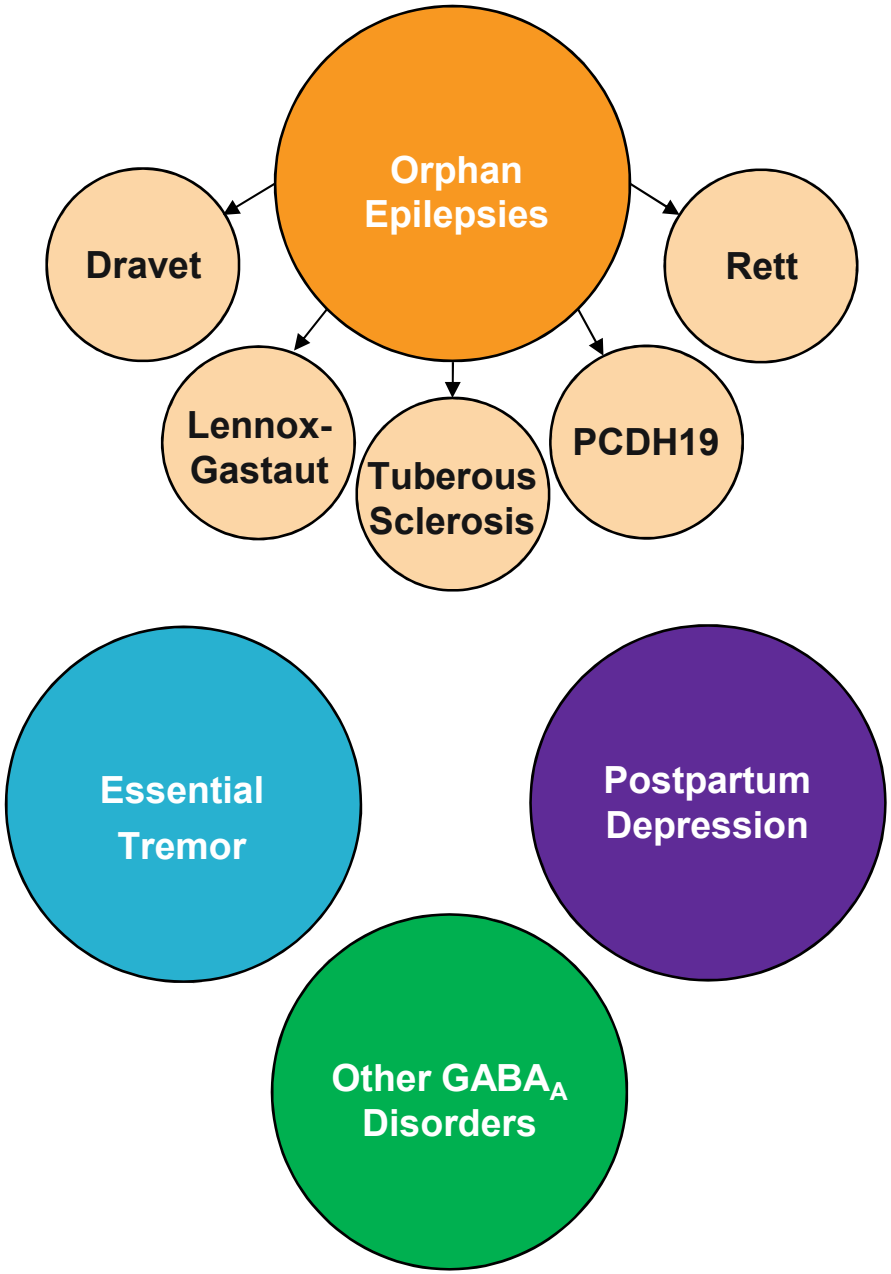
Postpartum Depression: Proof-of-Concept Observed in Exploratory Open-Label Study

- Abnormal GABAergic function has been associated with affective disorders
- Animal data suggest dramatic changes in expression of extrasynaptic $GABA_A$ receptors during perinatal period[1]
- Significant improvement of mean HAM-D scores in 4/4 PPD patients in Proof-of-Concept SAGE-547 study
- No SAEs: only AE reported in more than 1 patient was sedation (2 patients)
- Placebo-controlled study with SAGE-547 open for enrollment



[1] Licheri et al. *Neural Plasticity* 2015; Article ID 170435.

Potential to Develop SAGE-217 Across a Broad Range of $GABA_A$-Related Disorders



High Frequency Seizures Associated with Orphan Epilepsies

- Opportunity to target high frequency seizure phenotype across orphan epilepsies
- Severely impacts patients' lives with a large number of patients refractory to current treatments
- ~100,000 combined orphan epilepsy patients in U.S.[1]

Essential Tremor

- Debilitating neurological disorder that causes involuntary, rhythmic shaking with no known cause
- Current treatments only moderately effective
- ~10 million affected in U.S.[2]

Postpartum Depression

- Distinct and readily identified form of depression
- Potentially devastating consequences for mother and family
- ~800,000 mothers with perinatal mood disorders in U.S.[3]

Other $GABA_A$ Dysfunction-Related Disorders

[1] Company estimate; data on file
[2] International Essential Tremor Foundation website, http://www.essentialtremor.org/about-et/
[3] O'Hara MW, Wisner KL. Perinatal mental illness: definition, description and etiology. *Best Pract Res Clin Obstet Gynaecol* 2014;28(1):3-12.

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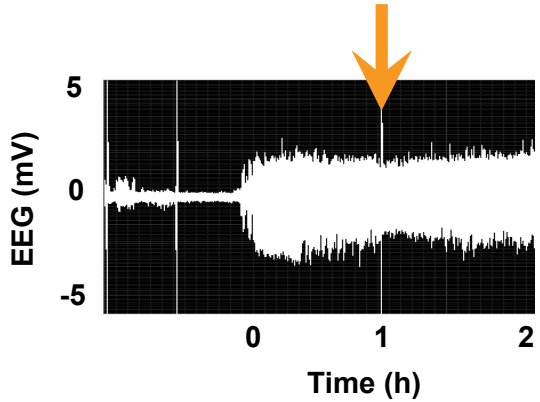
SAGE-689: Acute IV Treatment for Status Epilepticus

- Rapidly aborted seizure in pharmaco-resistant SE model
- Clean drug-drug interaction profile, wide therapeutic window
- Short half-life allows dose titration based on response
- Potential uses beyond SE

Diazepam Fails to Abort RSE
(60 min post-onset)

Lithium-pilocarpine rat model

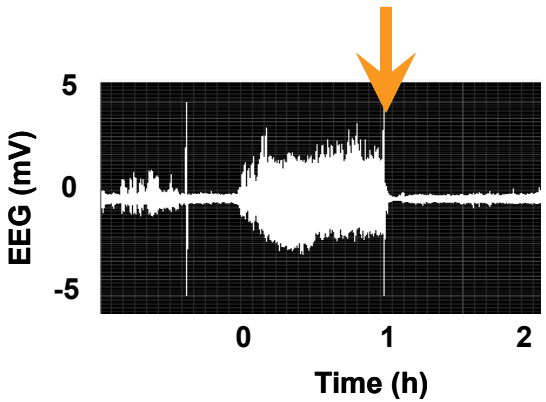
DZ (10 mg / kg *iv.*)



SAGE-689 Aborts RSE
(60 min post-onset)

Lithium-pilocarpine rat model

SAGE-689 (5 mg / kg *iv.*)

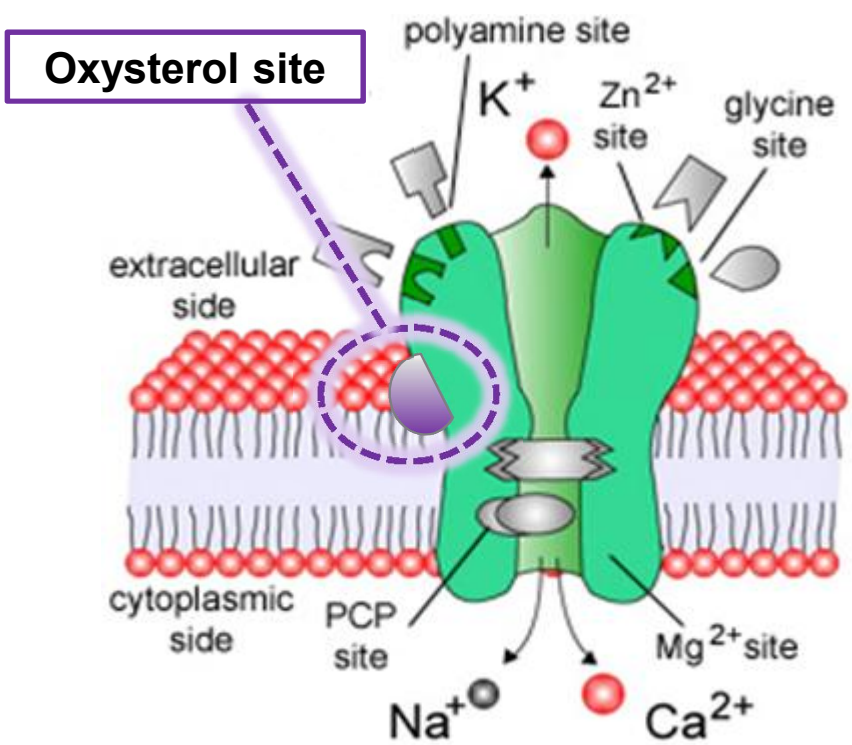


Next Generation NMDA Pipeline

NMDA: Opportunity to Unlock Therapeutic Activity of Novel Modulatory Mechanism

- NMDA receptor dysfunction implicated in multiple cognitive and mood disorders
- SAGE discovery of cerebrosterol as potent positive allosteric modulator of NMDA
- Acts at novel oxysterol NMDA receptor modulatory binding site

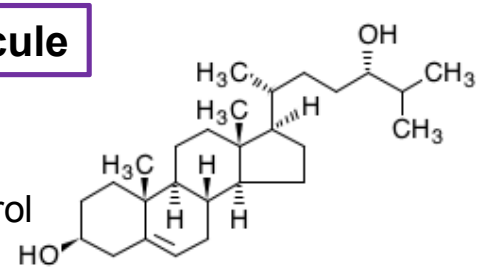
NMDA Receptor



SAGE NMDA Platform

Foundational molecule

Cerebrosterol
24(S)-Hydroxycholesterol



SAGE series of novel NMDA allosteric modulators with potential for:

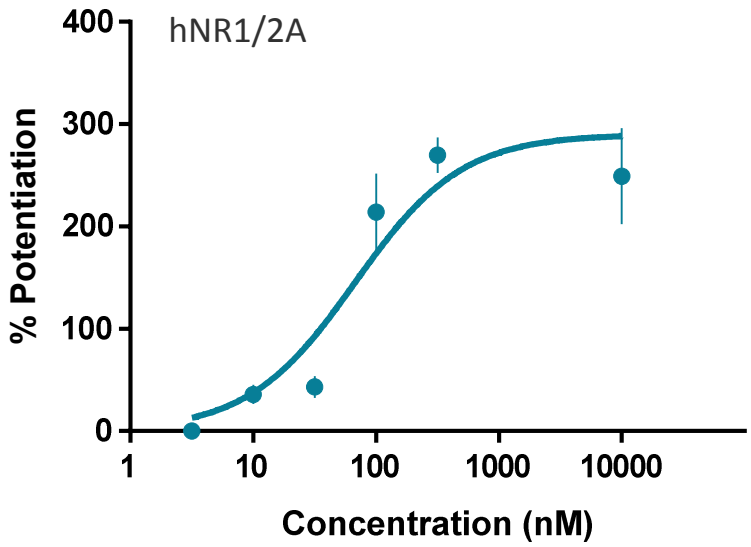
- Higher potency and receptor selectivity
- Better oral bioavailability
- Improved brain penetration

SAGE-718: Potential First-in-Class NMDA Modulator

- Potent oxysterol-based NMDA positive allosteric modulator
- Optimized PK profile designed for oral dosing
- Demonstrates robust activity in preclinical models of cerebrosterol deficit disorder and neuropsychiatric symptoms resulting from NMDA hypofunction

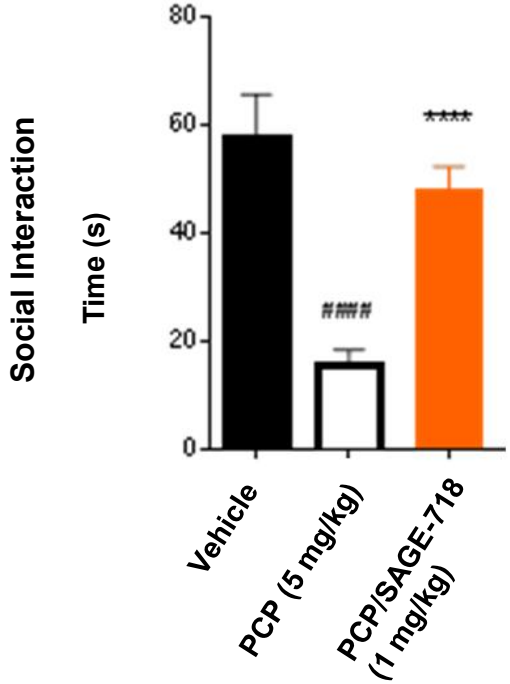
Activity at NMDA Receptors

SAGE-718 potent and selective positive modulation of NMDA Receptors



NMDA Hypofunction Model

SAGE-718 reverses social deficits associated with subchronic PCP treatment in vivo



Initial Focus on Biomarker-Defined Rare Diseases Characterized by NMDA Hypofunction

Smith-Lemli-Opitz Syndrome (SLOS)

- Metabolic disorder caused by mutations in the DHCR7 cholesterol synthesis gene
- Associated with significantly decreased plasma levels of cerebrosterol, suggesting that normal oxysterol-based NMDA modulation is disrupted
- Patients are affected by a broad range of neuropsychiatric and neurodevelopmental symptoms

Anti-NMDA Receptor Encephalitis (ANRE)

- Autoimmune disorder in which antibodies attack NMDA receptors
- Characterized by NMDA hypofunction
- Symptoms include a highly characteristic set of neuropsychiatric deficits, including cognitive and behavioral disturbances, movement disorders and loss of consciousness

- Currently no approved treatments for these orphan disorders
- Initial focus of SAGE-718 development to address neurological symptoms of these disorders through enhancing NMDA receptor function
- Potential to explore broader indications of NMDA receptor hypofunction for further study based on clinical biomarkers

Strong Foundation to Support Pipeline Growth

Strong Financial Position to Advance Programs

Q3 2015 Financial Results (as of 9/30/2015)

	Q3 '15	Q4 '14
Cash and Cash Equivalents	**$204.9M**	**$127.8M**

	Q3 '15	Q3 '14
Research & Development	$17.5M	$6.6M
General & Administrative	$6.6M	$2.9M
Net Loss	**$24.0M**	**$9.9M**

Guidance: Cash position expected to fund operations through mid-2017

Near-Term Clinical Milestones and Data Readouts Across Portfolio

- Developing SAGE-547 in Phase 3 trial in SRSE
- Advancing wholly-owned pipeline of first-in-class NCEs
- Establishing human proof-of-concept (PoC) data in broader CNS disorders
- Replicating $GABA_A$ strategy with NMDA portfolio

2H 2015 – Expected Milestones

- ✓ Phase 3 SPA agreement with FDA
- ✓ SAGE-547 PoC essential tremor data
- ✓ SAGE-217 Phase 1 initiation
- ✓ NMDA candidate selection
- ✓ SAGE-547 PoC PPD trial initiation

2016 – Expected Milestones

- SAGE-217 Phase 1 data
- SAGE-547 PoC PPD data
- SAGE-689 Phase 1 initiation
- SAGE-217 Phase 2 initiations
- SAGE-547 NDA planning