SAGE THERAPEUTICS™

Welcome to R&D Day 2016

Forward-Looking Statements

The slides presented today and the accompanying oral presentations 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,” “opportunity”, “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; anticipated development activities, milestones and results, including expected timing; the estimated number of patients with certain disorders or diseases; expectations regarding potential commercialization of our products, if successfully developed; the potential for expedited development and review for SAGE-547 in PPD as a result of the breakthough therapy designation; SAGE’s belief in the sufficiency of the current Phase 3 trial, if succcessful, for approval in the E.U.; potential future indications for SAGE’s product candidates; other planned activities; SAGE’s strategy and business outlook; 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 early stage clinical trials may not be repeated or observed in ongoing or future studies 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;
- decisions or actions of regulatory agencies may affect the initiation, timing and progress of clinical trials, or SAGE’s ability to obtain marketing approval for its product candidates, and a regulatory authority may ultimately decide that the design or results of our clinical trials are not sufficient for regulatory approval despite earlier guidance;
- we may continue to experience slower than expected enrollment in the STATUS trial or may encounter other delays or problems, including in analyzing data or requiring the need for additional analysis, data or patients, and we may experience these types of enrollment issues and other delays and problems in our other trials, and such issues with any trial could cause delay in completion of the trial, availability of results and timing of future activities;
- even if SAGE’s products are successfully developed and approved, the number of patients with the diseases or disorders our products treat, and the actual market for such products may be smaller than SAGE’s current estimates;
- 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’s operating expenses may be higher than forecasted and SAGE may also face unexpected expenditures or decide to expand our activities, 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 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 our most recent Quarterly Report on Form 10-Q, 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.

Today's Guest Speakers

Eric Rosenthal, MD

MASSACHUSETTS GENERAL HOSPITAL
NEUROLOGY

Associate Director of the Neurosciences Intensive Care Unit

Director, Neurocritical Care Fellowship Training Program

Director, Critical Care Neuromonitoring

Samantha Meltzer-Brody, MD, MPH

UNC SCHOOL OF MEDICINE

Associate Professor, Associate Chair for Faculty Development

Director, Perinatal Psychiatry Program

Director, Taking Care of Our Own Program

Today's Sage Speakers

Jeff Jonas, MD
Chief Executive Officer

Steve Kanes, MD, PhD
Chief Medical Officer

Al Robichaud, PhD
Chief Scientific Officer

Jim Doherty, PhD
SVP, Research

Agenda

Topic	Presenter
Introduction	Jeff Jonas, MD – Chief Executive Officer
Sage's Foundational Science	Al Robichaud, PhD – Chief Scientific Officer
Translational Neuroscience	Jim Doherty, PhD – SVP, Research
Q&A	
SAGE-547 Clinical & Regulatory Strategy	Steve Kanes, MD, PhD – Chief Medical Officer
SAGE-547 in SRSE	Eric Rosenthal, MD, Massachusetts General Hospital
SAGE-547 in PPD	Samantha Meltzer-Brody, MD, MPH, UNC Center for Women's Mood Disorders
SAGE-217: A First-in-Class Oral Modulator	Steve Kanes, MD, PhD – Chief Medical Officer
Conclusion	Jeff Jonas, MD – Chief Executive Officer
Q&A	

SAGE THERAPEUTICS™

Introduction

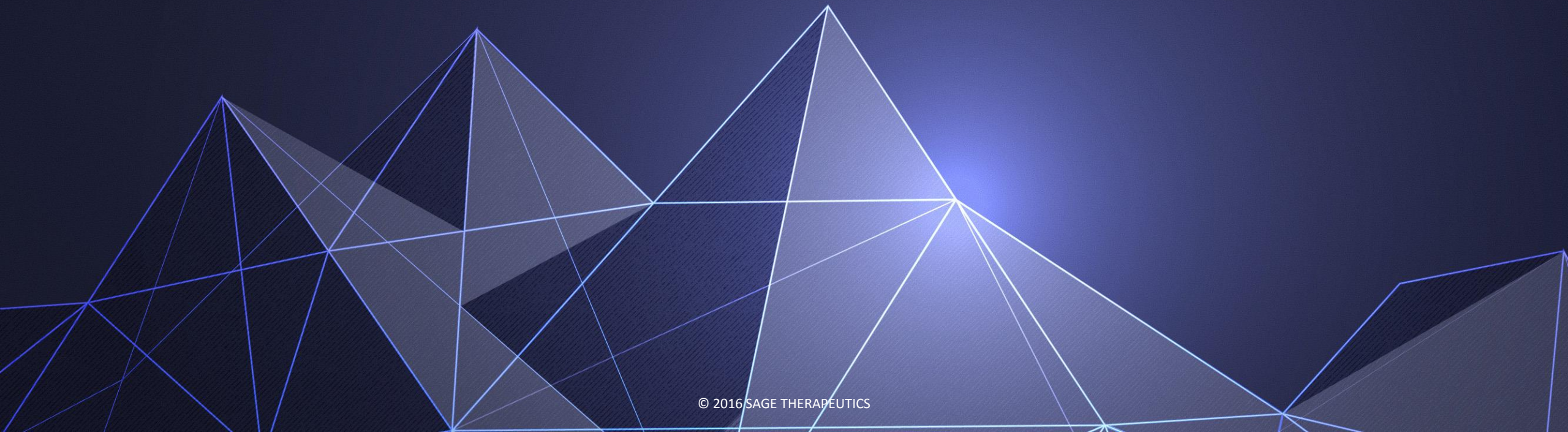
Jeff Jonas, MD - CEO

The CNS Disease Landscape

The brain is an interactive network. Simple “target” approaches may fail.

Few CNS breakthroughs in decades.

CNS disorders represent 35% of WW disease burden.



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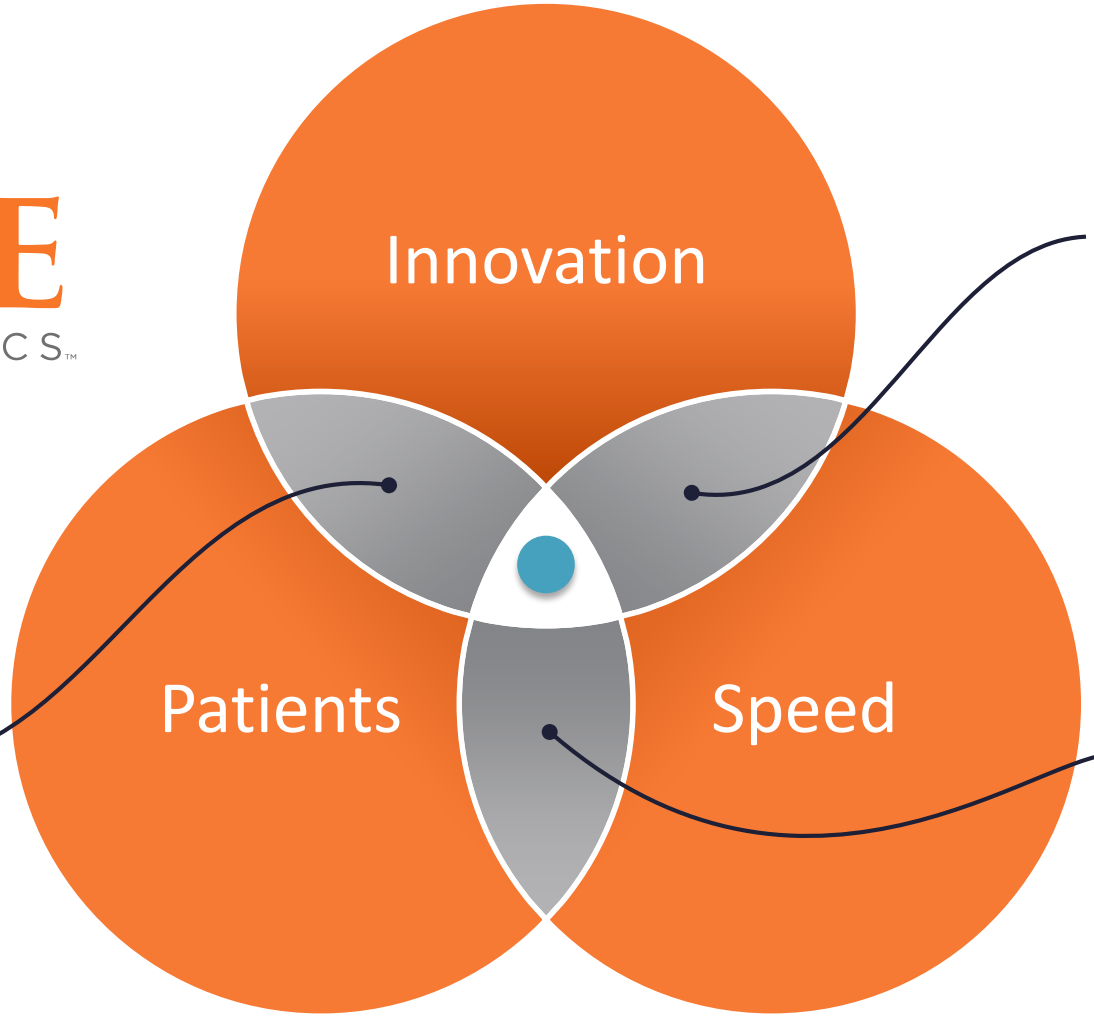
RETHINKING CNS

SAGE THERAPEUTICS

Commitment to Being a Neuroscience Leader

SAGE THERAPEUTICS™



Advancing novel medicines through deliberate, stepwise and data-driven development

Tackling the **innovation** gap in CNS

Responsibly pursuing **expedited pathways** to deliver new treatments

Pioneer New Approaches to Neuroscience R&D

- **Lead with human data**
- Focus on **powerful mechanisms** known to have demonstrated and broad effects on brain networks
- Design **bespoke next-generation compounds** differentiated from available therapies
- Utilize new and efficient **translational approaches** to speed discovery and clinical development
- **Data-driven development** - true “serial de-risking” to “incrementally innovate”
- Clinical trials in **defined populations** with **rapid readouts** and **well-defined endpoints**

Sage Data and Pipeline Support Broad Focus on Neuropsych

	Neurology	Mood Disorders	Movement Disorders
Clinical Focus	• SRSE • NMDA Hypofunction	• Postpartum Depression • Major Depressive Disorder	• Essential Tremor • Parkinson’s Disease
Exploratory	• Orphan Epilepsies • Autism Spectrum • Sleep • Cognition • Huntington’s • Alzheimer's	• Treatment-Resistant Depression • Anxiety • Mania • Bipolar Disorder • Panic Disorder	

Multi-Compound Neuropsych Portfolio

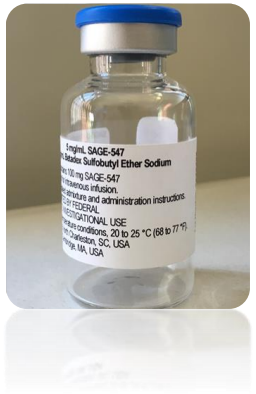
Program	Compound	Indication	Preclinical	Phase 1	Phase 2	Phase 3
GABA	SAGE-547	Super-Refractory Status Epilepticus				
		Postpartum Depression				
	SAGE-217	Postpartum Depression				
		Major Depressive Disorder				
		Essential Tremor				
		Parkinson's Disease				
	SAGE-689	Status Epilepticus/Undisclosed				
	SAGE-105	Orphan Epilepsies				
	SAGE-324	GABA Hypofunction				
NMDA	SAGE-718	Cerebrosterol Deficit Disorders				
		Anti-NMDA Receptor Encephalitis				
		NMDA Hypofunction				

Sage's Progress

SAGE THERAPEUTICS

2011 — Sage Launched – $35M Series A

2012 — First SAGE-547 SRSE Emergency Use



2013 — First GABA IND Filing

2014 — Phase 1/2 SRSE Initiation; Sage Completes IPO

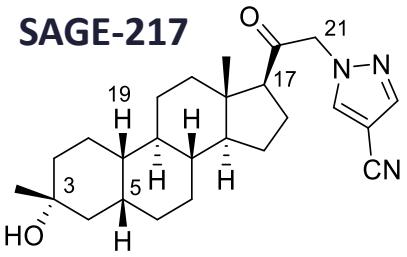
2015 — Phase 3 SRSE Initiation; SAGE-217 First-in-Human

2016 — Phase 3 PPD Initiation; Initiation of SAGE-217 Phase 2 Programs

2017 — 8 Expected Clinical Data Readouts; First NMDA IND Filing Expected

2018 — Planned SAGE-547 Commercial Launch

SAGE-217



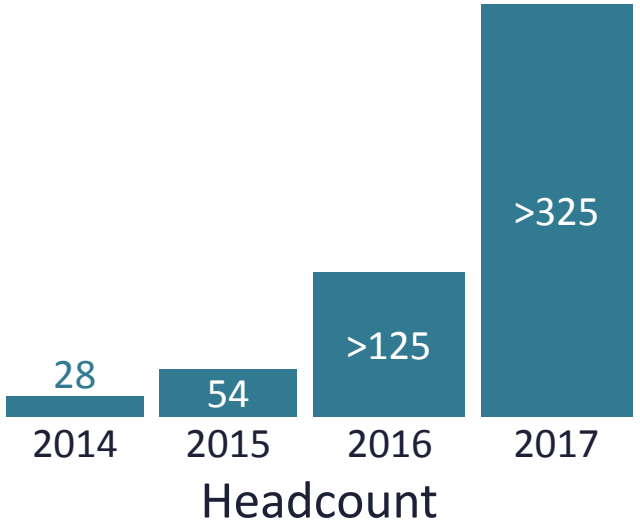
Abbreviation: SRSE, super-refractory status epilepticus.

Sage's Growth

Building an Experienced Team with Leading Capabilities to Execute on Our Vision

Significant investments in:

- Research & Discovery
- Clinical Development
- Medical Affairs
- Commercial & Tech Ops



Key Recent Hires:

- Ryan Arnold, DO - VP, Medical Affairs
- Anne Marie Cook - SVP, General Counsel
- Ian Hunt - VP, Global Head of Market Access
- Joe McGrath - VP, Information Technologies
- Rob Pawliuk, PhD - VP, Non-Clinical Dev.
- AJ Sankoh, PhD - VP, Biometrics
- Heinrich Schlieker, PhD - SVP, Tech Ops
- Kendyl Schaefer - VP, Program Management

Biogen · Sanofi Genzyme · Aegerion Pharmaceuticals · Biogen · Sanofi Genzyme · UCB Pharma · Forum Pharmaceuticals · Sunovion · Cubist · Sanofi Genzyme · Synageva BioPharma · Vertex · Cubist · Roche · Shire · Sunovion

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Sage Today

Leadership in CNS Development

- Robust pipeline of differentiated and novel GABA and NMDA drug candidates

SAGE-547 **Opportunities**

- Two parallel Phase 3 programs in SRSE and PPD with upcoming data readouts

Developing SAGE-217

- First-in-class extrasynaptic GABA oral modulator
- Multiple Phase 2 studies with opportunities in large CNS markets

Uniquely **Positioned**

- 8 data readouts across pipeline with optionality for portfolio expansion
- Value inflection opportunities and continued momentum expected in 2017

Our goal: commercial CNS product portfolio with global reach

Abbreviation: CNS, central nervous system; GABA, γ-aminobutyric acid; NMDA, *N*-Methyl-D-aspartic acid; SRSE, super-refractory status epilepticus; PPD, postpartum depression.

SAGE THERAPEUTICS™

OUR MISSION is to make life better for patients with CNS diseases by discovering, developing, and delivering important new medicines to patients in need.

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Sage's Foundational Science

Al Robichaud, PhD – CSO

…Why GABA and NMDA?

Targeting Regulatory Neural Networks

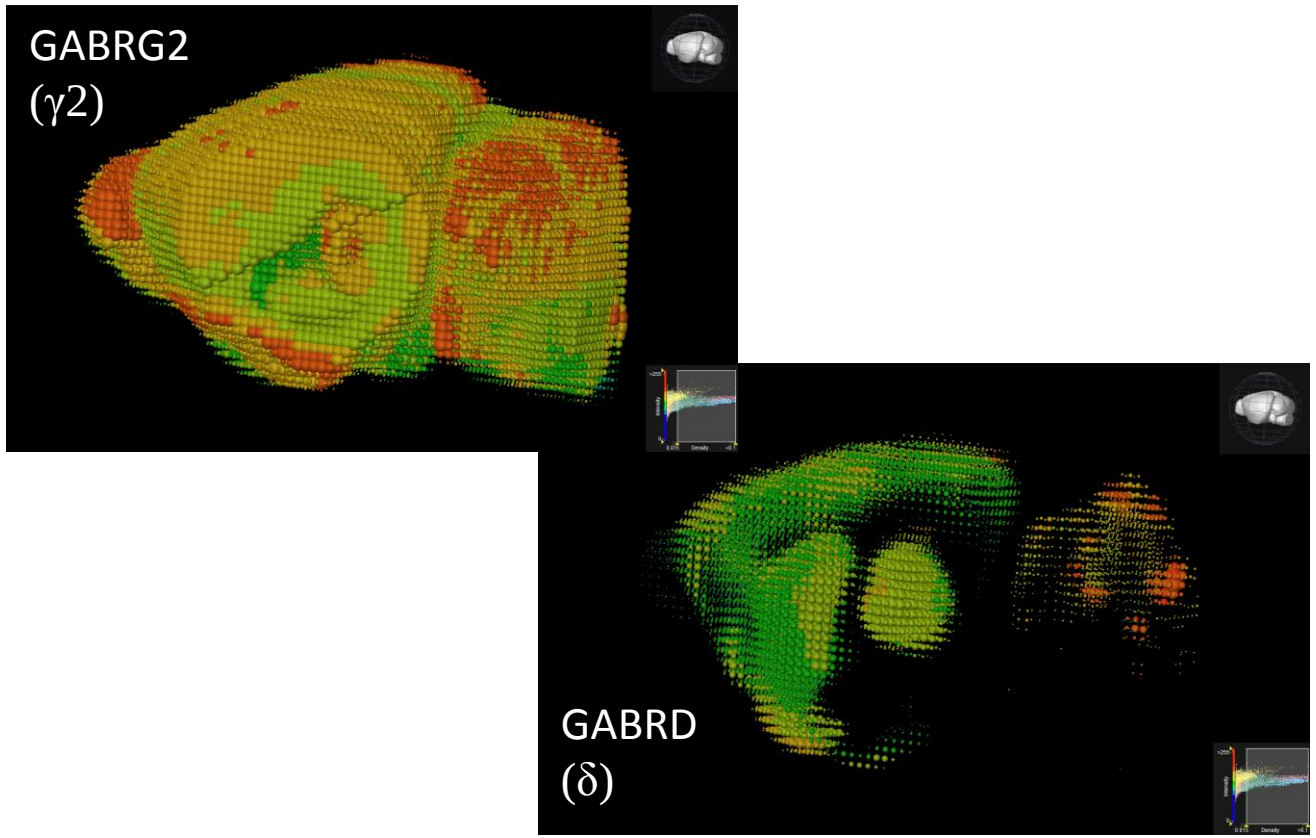
- Key brain function controlled via a complex balance of excitation/inhibition circuitry
  - System disruption during aging and in disease
  - Understanding of brain circuitry to impact disease state
- Proven mechanisms in multiple therapies
  - GABAergic (benzodiazepines), channel modulators
- Opportunity to differentiate significantly with neuroactive steroid GABA and NMDA modulators
  - Designed for purpose NCEs

GABA is the Major Inhibitory Brain Network

- GABA is an abundant and ubiquitous inhibitory neurotransmitter in the brain
  - Present in 30-50% of all neurons[1]
- GABA dysfunction can occur in many different brain regions with potential downstream effects
- The $GABA_A$ receptor family is complex with diverse physiology, pharmacology and function[2]:
  - 19 different receptor subunits[3]
  - Brain region and neuronal circuit
  - Synaptic location

$GABA_A$ Receptors are Prevalent throughout the Brain

Synaptic and extrasynaptic $GABA_A$ receptors in mouse brain[3]

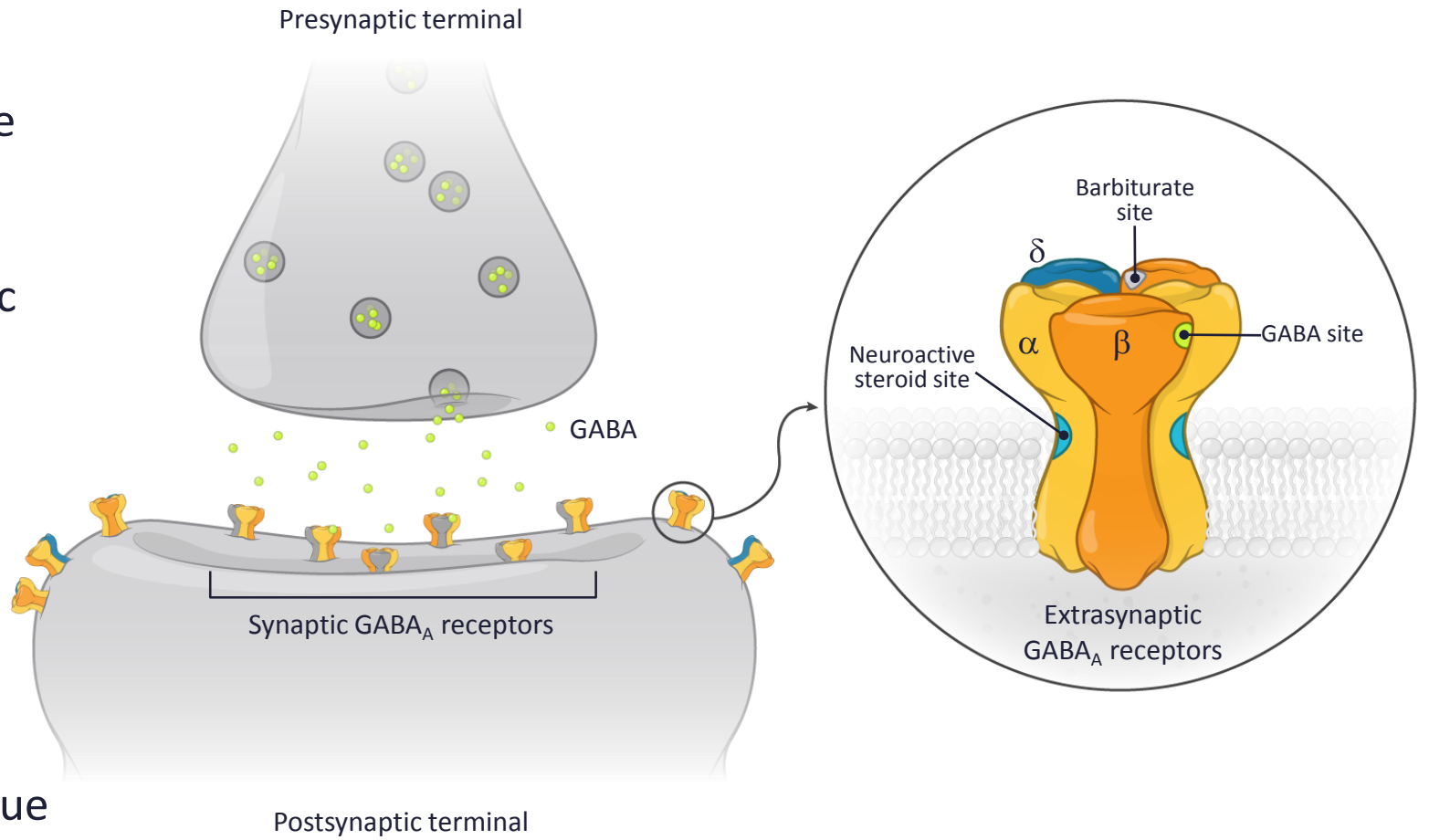


1,2. Nutt DJ, Malizia AL, *Br J Psychiatry*, 2001; 3. Olsen RW, Sieghart W, *Neuropharmacoloy*, 2009; 3. Image Credit: Allen Institute.

…Why Not Just Another Benzo?

Sage's GABA Compounds Specifically Target both Phasic and Tonic Receptors

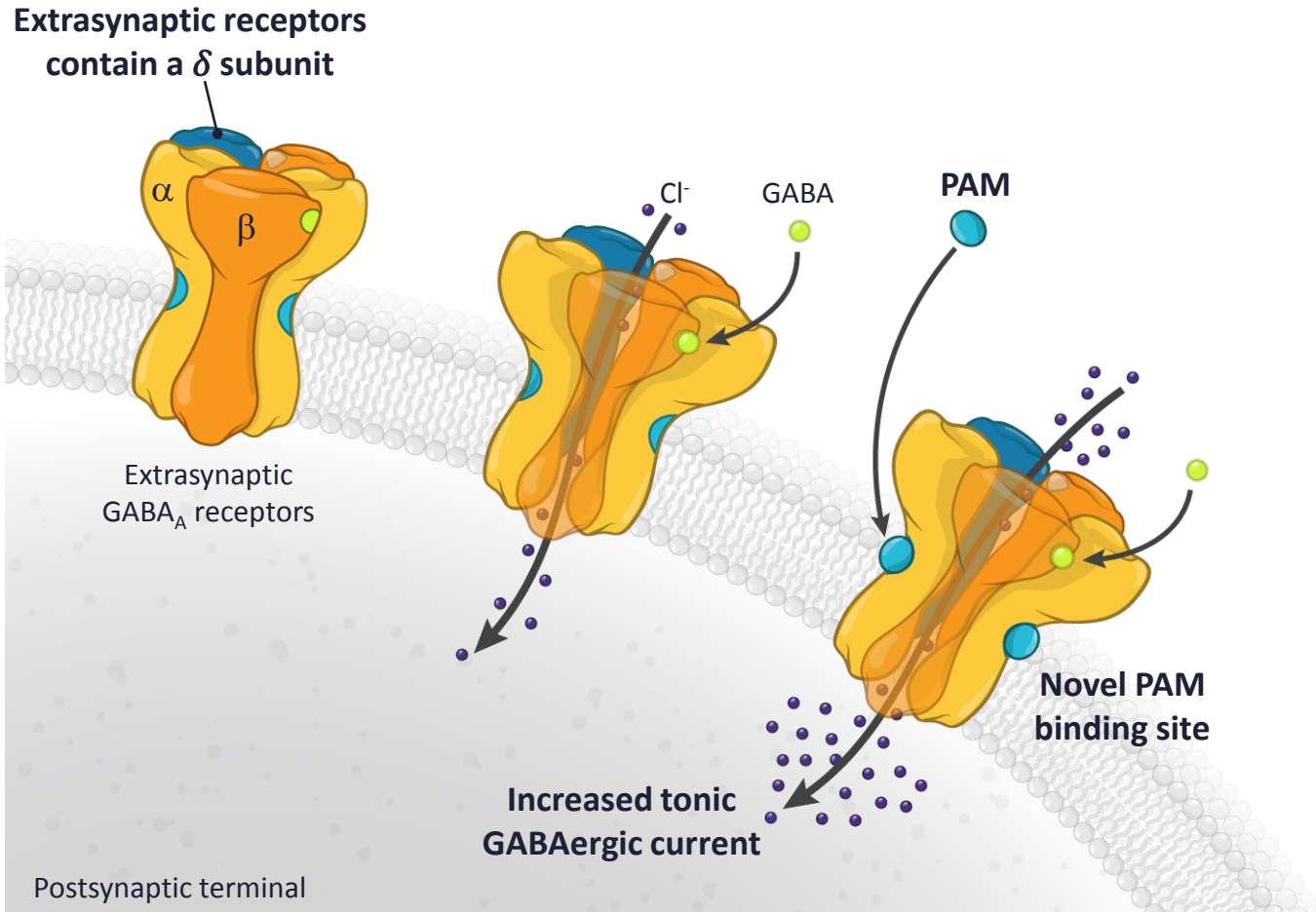
- **Neuroactive steroids** (NAS) can enhance neurotransmission in both regions, unlike benzodiazepines
- Synaptic $GABA_A$ receptors mediate phasic inhibition and **extrasynaptic** receptors regulate tonic inhibition
- **Tonic inhibition** plays a critical role in regulating neuronal circuit excitability
  - Potential to treat multiple diseases not accessible with benzodiazepines
- **Sage NAS compounds** demonstrate unique capability to increase receptor function
  - PKC trafficking of receptors to cell surface



…Why Allosteric Modulation?

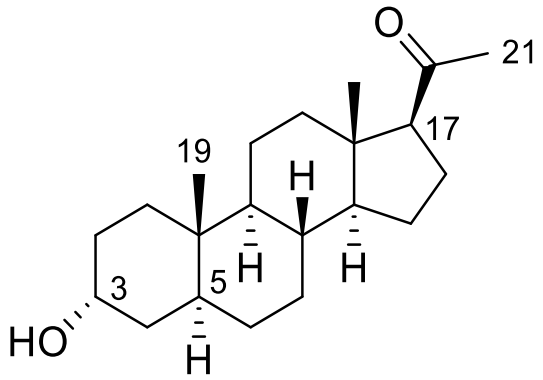
Potential to Restore Receptor Function with Better Drug Property Profiles

- **Positive allosteric modulation (PAM)** increases receptor efficacy and/or potency
- Fine tunes receptor activity without overstimulation
  - Direct gating compounds can't do this
- Offers potential for significant advantages, high selectivity and minimal off-target effects

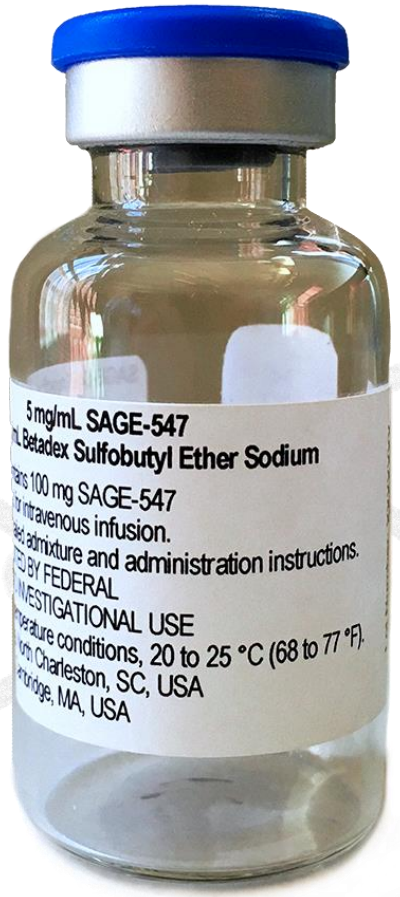


SAGE-547: Gateway to Portfolio of Drug Candidates

First Generation Compound from Sage's Robust GABA Library



- **SAGE-547 Injection** is a proprietary formulation of allopregnanolone
- Endogenous PAM of $GABA_A$ receptors[1]
- Positive data across numerous clinical and preclinical studies
  - Antiseizure
  - Antiepileptic
  - Anxiolysis
  - Mood disorders
  - Movement disorders

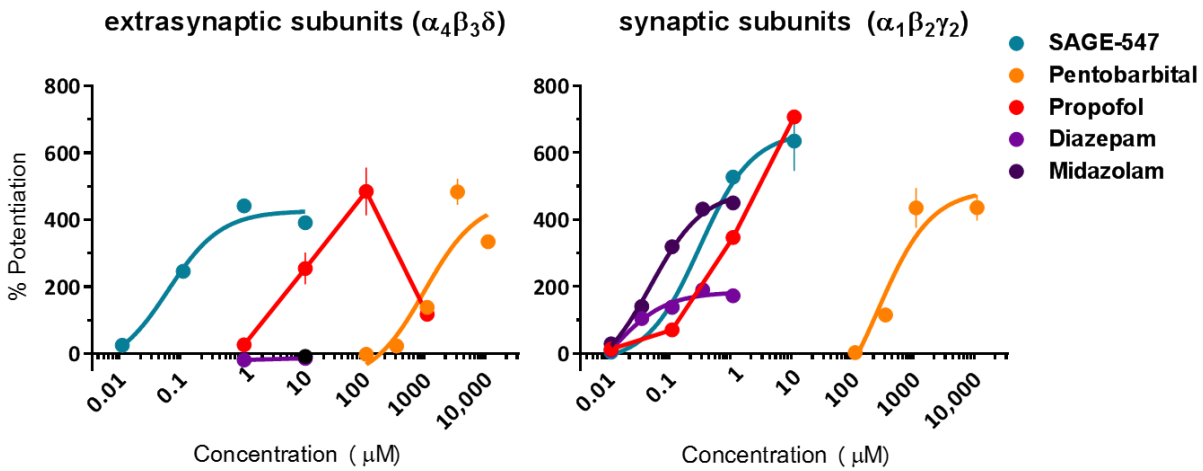


1. Majewska et al, *Science*, 1986.

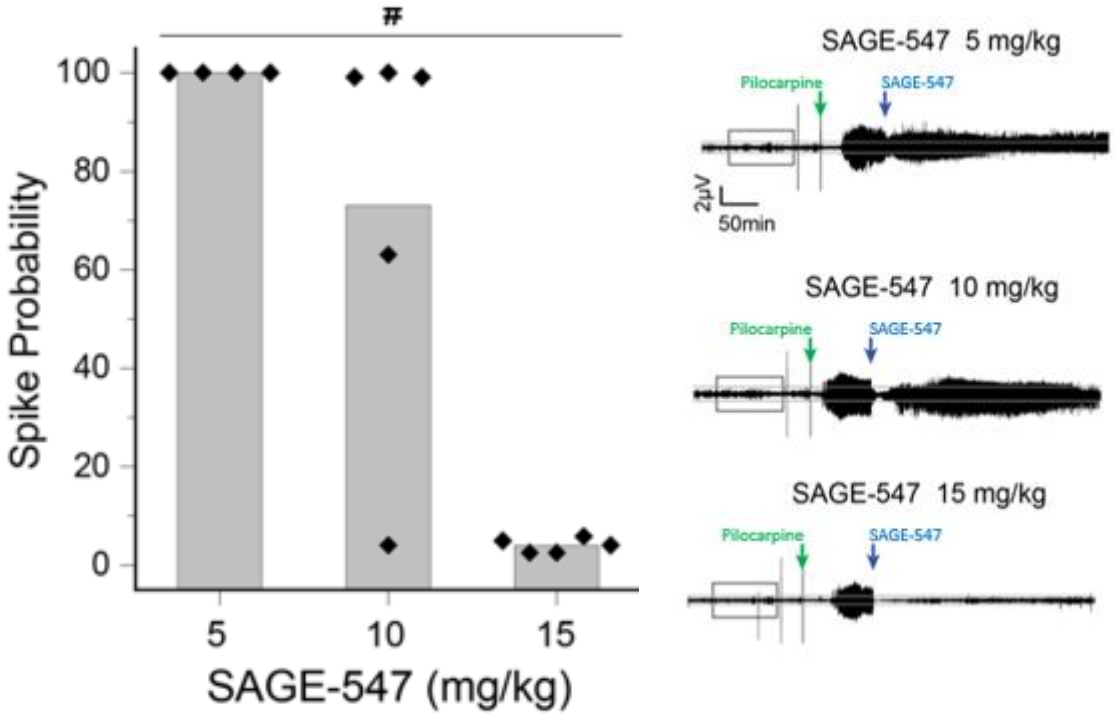
SAGE-547: Robust Activity in Preclinical Models

Potently Modulates Extrasynaptic $GABA_A$ Receptors and Halts Benzo-Resistant RSE

SAGE-547 Significantly More Potent and Selective at Extrasynaptic $GABA_A$ Receptors than Other Modulators (*in vitro*)[1]



SAGE-547 Halts Benzo-Resistant RSE in Lithium Pilocarpine Rat Model (*in vivo*)[1]



1. Ackley et al, Society for Neuroscience Annual Meeting, 2016.

…Why Develop Novel NAS $GABA_A$ Allosteric Modulators?

Pre-Sage Status of NAS Knowledge Base

- NAS class undruggable (orally)
- Poor understanding of the pharmacology
- Difficult to measure biologic activity
- NAS hard to synthesize
- Poor solubility, hard to formulate
- Little or no bioavailability
- Crowded chemical space, IP limitations

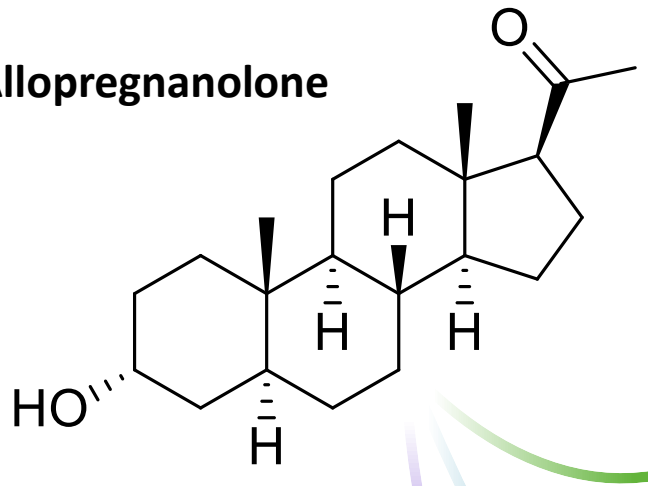
Sage Developments and Proprietary Advancement of NAS Platform

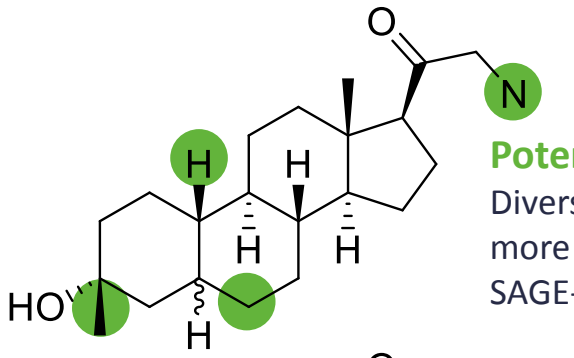
- SAGE-217, SAGE-105, SAGE-324, SAGE-689…
- New discoveries of utility of extrasynaptic receptors; receptor trafficking properties
- Well developed high throughput assays
- Rapid efficient synthesis with access to all areas of scaffold for SAR
- Developed formulations for iv, im, po of multiple compounds (solution and solid)
- Highly bioavailable, fit for purpose
- Expected broad coverage of new chemical space

Sage's $GABA_A$ Modulator Capabilities

Allopregnanolone SAR is Basis for Diverse New Chemical Entities (NCE)

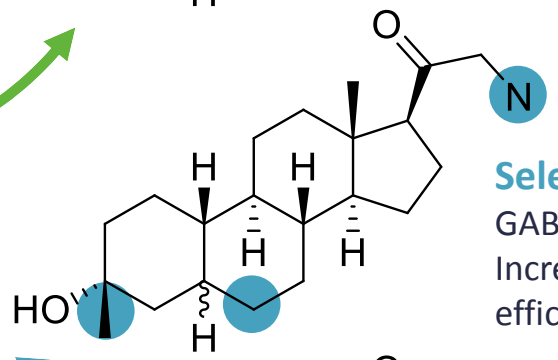
Allopregnanolone





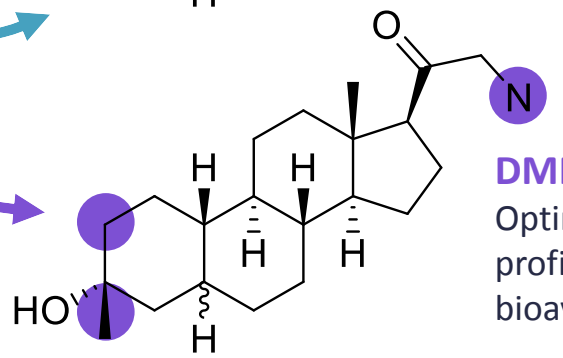
Potency/Efficacy

Diverse library of compounds more potent (*in vitro*) than SAGE-547



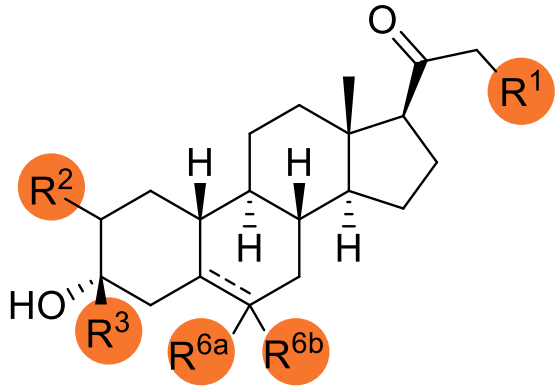
Selectivity

GABA alpha 1 vs alpha 4
Increased potency and efficacy in preclinical models



DMPK

Optimized formulations and PK profiles with excellent bioavailability

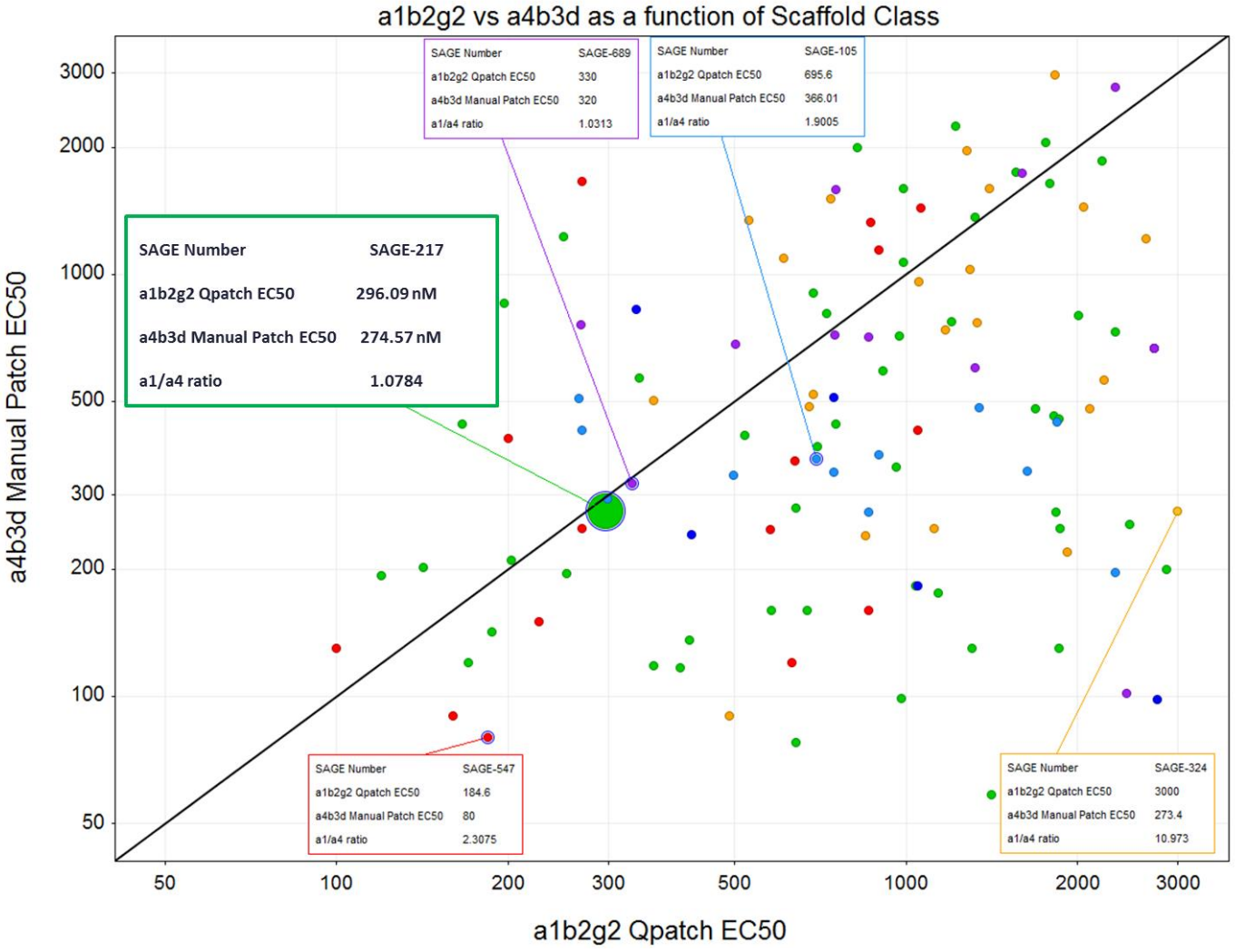


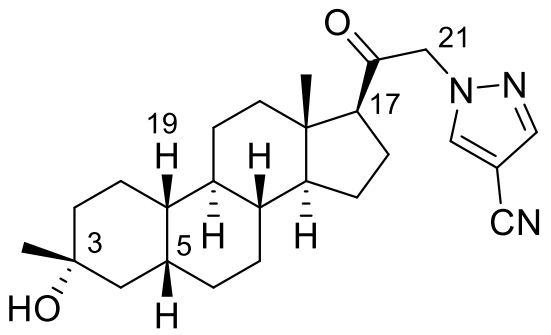
IP

Robust library of ~1,800 NCEs
Growing IP portfolio

Sage has Created a Leading GABA Compound Library

Over 1,800 Diverse Compounds with Differentiated PK/PD Profiles and Receptor Selectivity



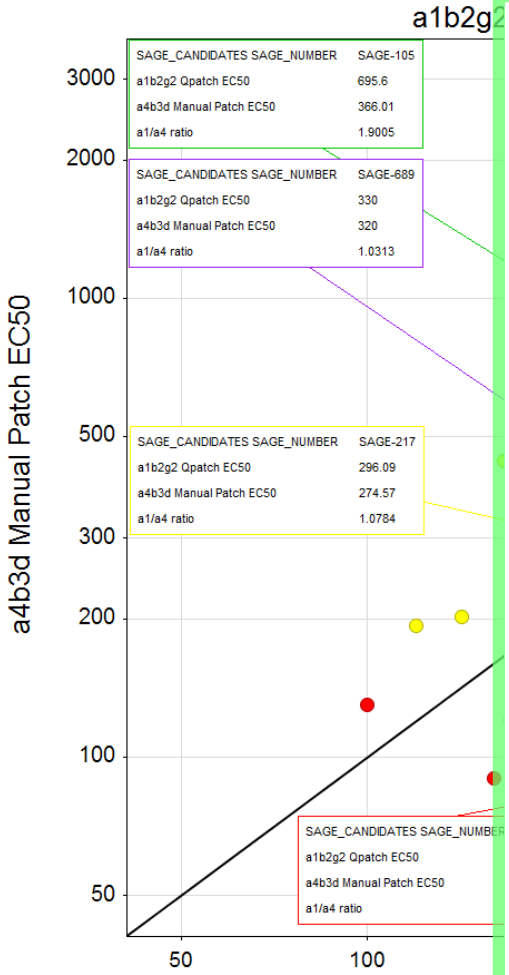


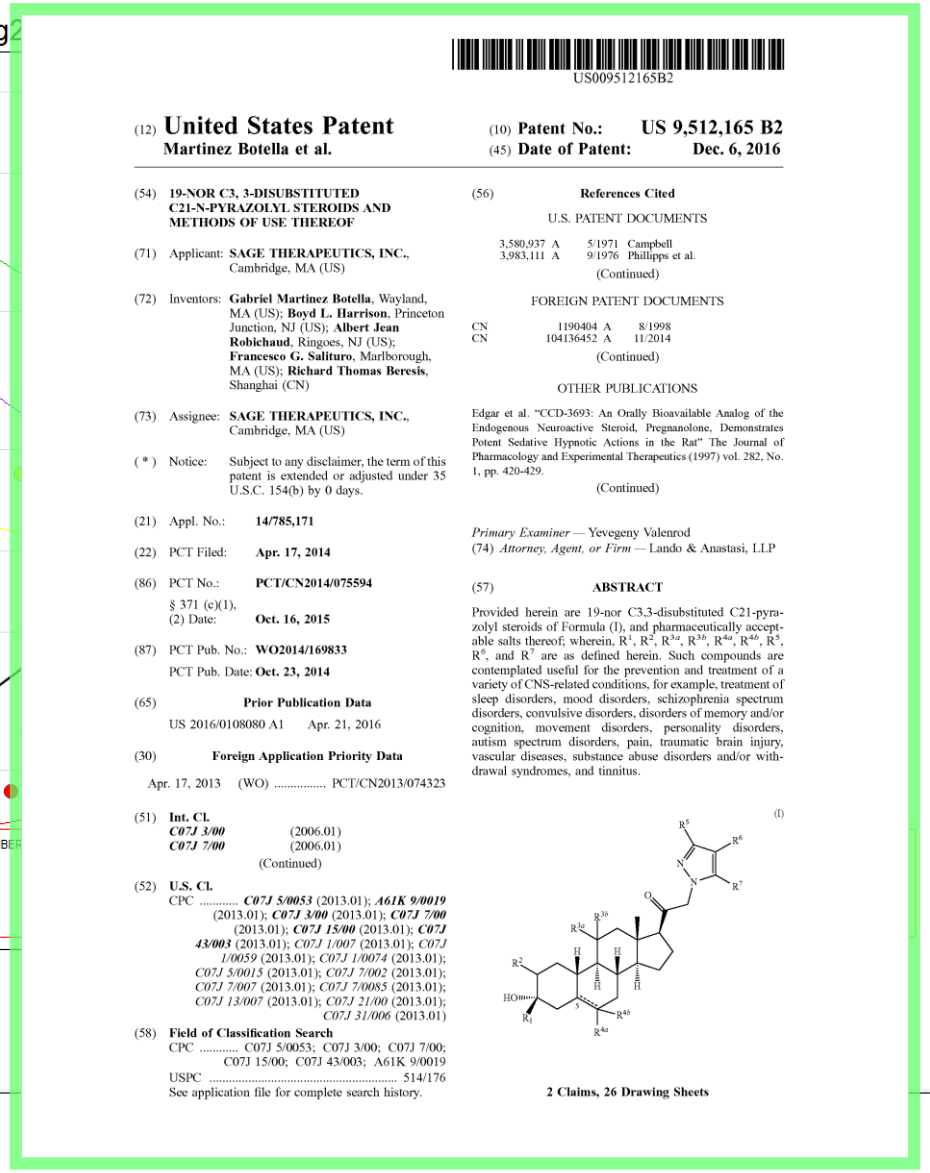
SAGE-217 - lead oral clinical program:

- Pharmacological similarity to SAGE-547
- Optimized oral PK profile

Sage has Created a Leading GABA Compound Library

Over 1,800 Diverse Compounds with Differentiated PK/PD Profiles and Receptor Selectivity





US009512165B2

(12) **United States Patent**
Martinez Botella et al.

(10) **Patent No.: US 9,512,165 B2**
(45) **Date of Patent: Dec. 6, 2016**

(54) **19-NOR C3, 3-DISUBSTITUTED C21-N-PYRAZOLYL STEROIDS AND METHODS OF USE THEREOF**

(71) Applicant: **SAGE THERAPEUTICS, INC.**, Cambridge, MA (US)

(72) Inventors: **Gabriel Martinez Botella**, Wayland, MA (US); **Boyd L. Harrison**, Princeton Junction, NJ (US); **Albert Jean Robichaud**, Ringoes, NJ (US); **Francesco G. Salituro**, Marlborough, MA (US); **Richard Thomas Beresis**, Shanghai (CN)

(73) Assignee: **SAGE THERAPEUTICS, INC.**, Cambridge, MA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **14/785,171**

(22) PCT Filed: **Apr. 17, 2014**

(86) PCT No.: **PCT/CN2014/075594**
§ 371 (c)(1),
(2) Date: **Oct. 16, 2015**

(87) PCT Pub. No.: **WO2014/169833**
PCT Pub. Date: **Oct. 23, 2014**

(65) **Prior Publication Data**
US 2016/0108080 A1 Apr. 21, 2016

(30) **Foreign Application Priority Data**
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(51) **Int. Cl.**
C07J 3/00 (2006.01)
C07J 7/00 (2006.01)
(Continued)

(52) **U.S. Cl.**
CPC ***C07J 5/0053*** (2013.01); ***A61K 9/0019*** (2013.01); ***C07J 3/00*** (2013.01); ***C07J 7/00*** (2013.01); ***C07J 15/00*** (2013.01); ***C07J 43/003*** (2013.01); *C07J 1/007* (2013.01); *C07J 1/0059* (2013.01); *C07J 1/0074* (2013.01); *C07J 5/0015* (2013.01); *C07J 7/002* (2013.01); *C07J 7/007* (2013.01); *C07J 7/0085* (2013.01); *C07J 13/007* (2013.01); *C07J 21/00* (2013.01); *C07J 31/006* (2013.01)

(58) **Field of Classification Search**
CPC C07J 5/0053; C07J 3/00; C07J 7/00; C07J 15/00; C07J 43/003; A61K 9/0019
USPC 514/176
See application file for complete search history.

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(Continued)

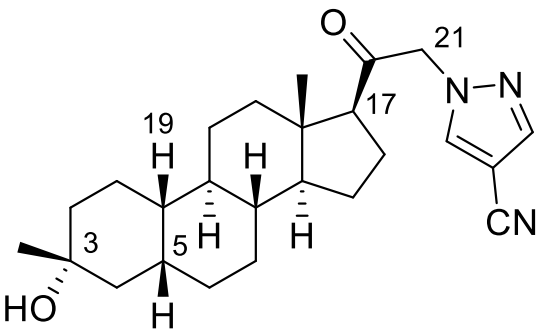
Primary Examiner — Yevegeny Valenrod
(74) *Attorney, Agent, or Firm* — Lando & Anastasi, LLP

(57) **ABSTRACT**

Provided herein are 19-nor C3,3-disubstituted C21-pyrazolyl steroids of Formula (I), and pharmaceutically acceptable salts thereof; wherein, R^1, R^2, R^{3a}, R^{3b}, R^{4a}, R^{4b}, R^5, R^6, and R^7 are as defined herein. Such compounds are contemplated useful for the prevention and treatment of a variety of CNS-related conditions, for example, treatment of sleep disorders, mood disorders, schizophrenia spectrum disorders, convulsive disorders, disorders of memory and/or cognition, movement disorders, personality disorders, autism spectrum disorders, pain, traumatic brain injury, vascular diseases, substance abuse disorders and/or withdrawal syndromes, and tinnitus.

(I)

2 Claims, 26 Drawing Sheets



SAGE-217 - lead oral clinical program:

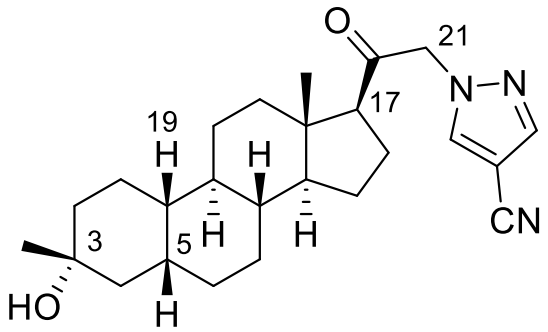
- Pharmacological similarity to SAGE-547
- Optimized oral PK profile
- Issued Patent US 9,512,165

SAGE THERAPEUTICS

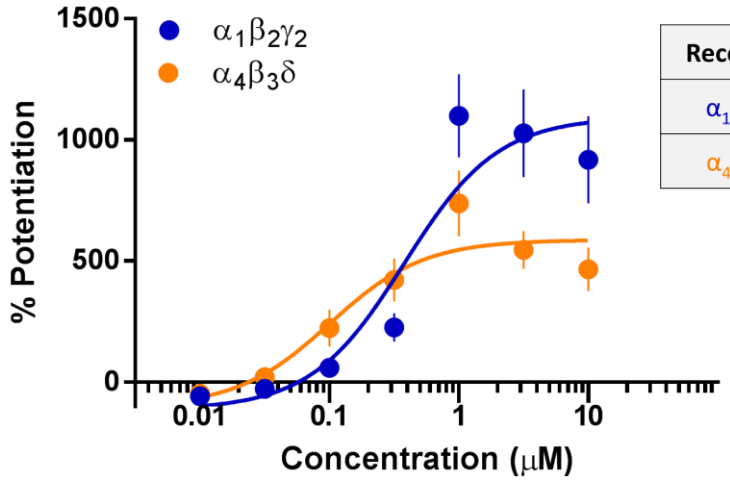
SAGE-217: First-in-Class Oral $GABA_A$ Receptor Modulator

Novel Compound Entering Broad Phase 2 Development

- Well tolerated in over 100 human subjects in Phase 1
- In preclinical studies:
  - Highly potent and selective next generation $GABA_A$ receptor PAM
  - PK/PD profile strongly differentiated from 1st Gen NAS
  - Oral bioavailability
  - Brain penetrant in preclinical studies (B/P > 3)

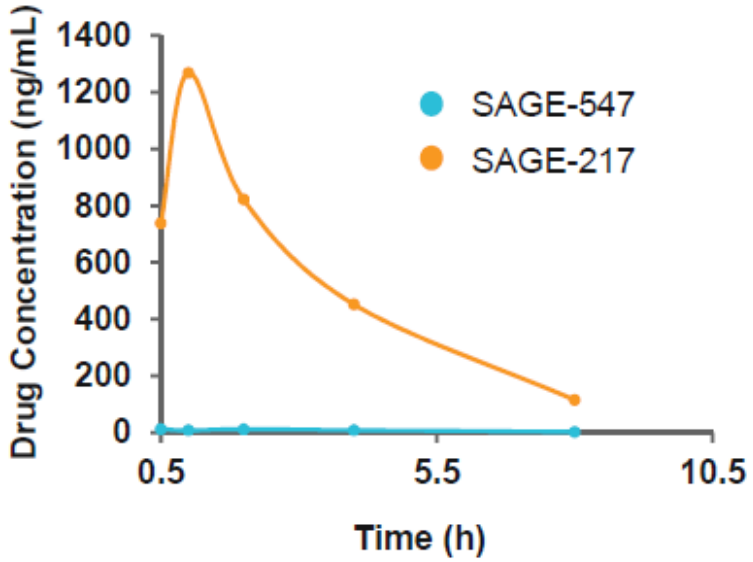


Potent Activity at $GABA_A$ Receptors (*in vitro*)[1]



Receptor	EC_{50} (nM)	Emax (%)
$\alpha_1\beta_2\gamma_2$	374	1041
$\alpha_4\beta_3\delta$	163	640

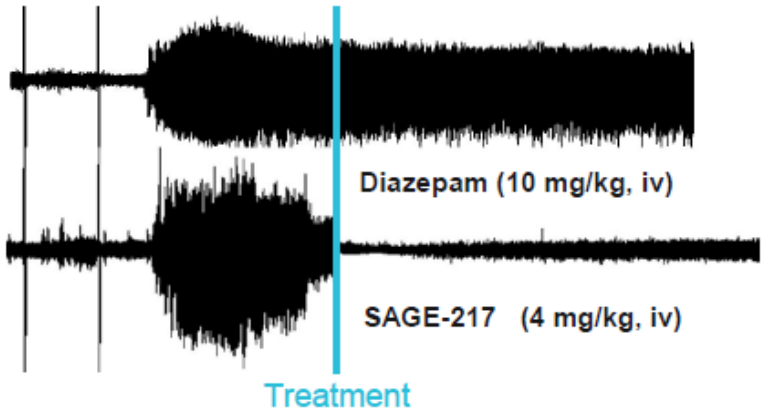
Oral Bioavailability vs. SAGE-547 (*in vivo*) [1]



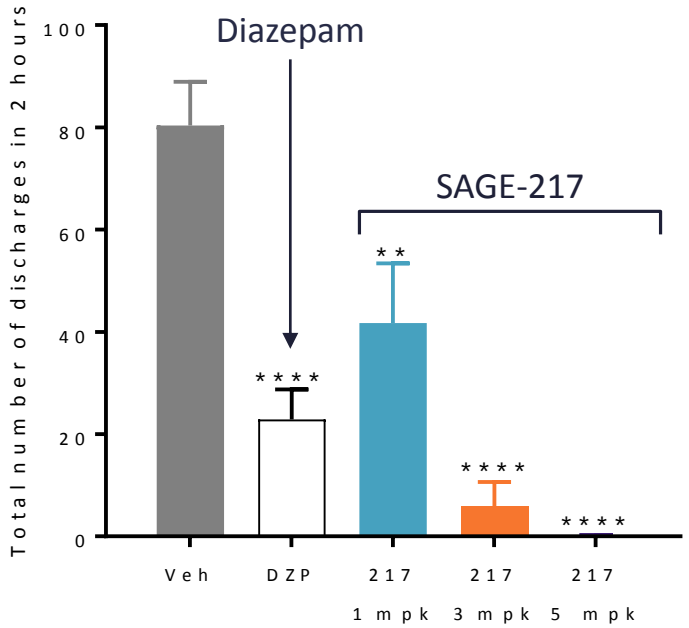
1. Belfort et al, American Epilepsy Society Annual Meeting, 2016.

SAGE-217: Robust Activity Across Broad Range of Preclinical Seizure Models

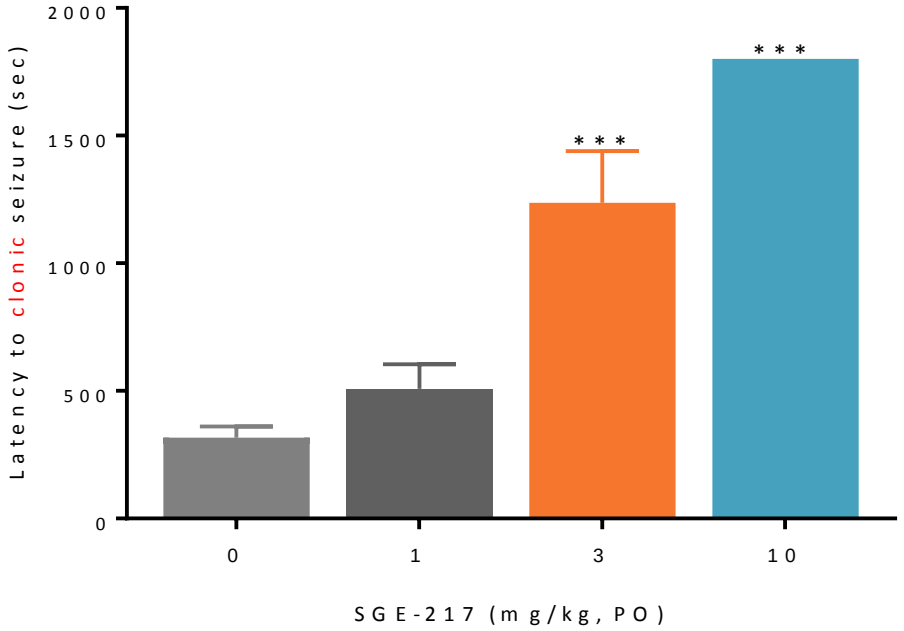
Halts SE in Pharmaco-Resistant Lithium Pilocarpine Model



Dose-Dependent Anti-Seizure Effect in MTLE Model[1]



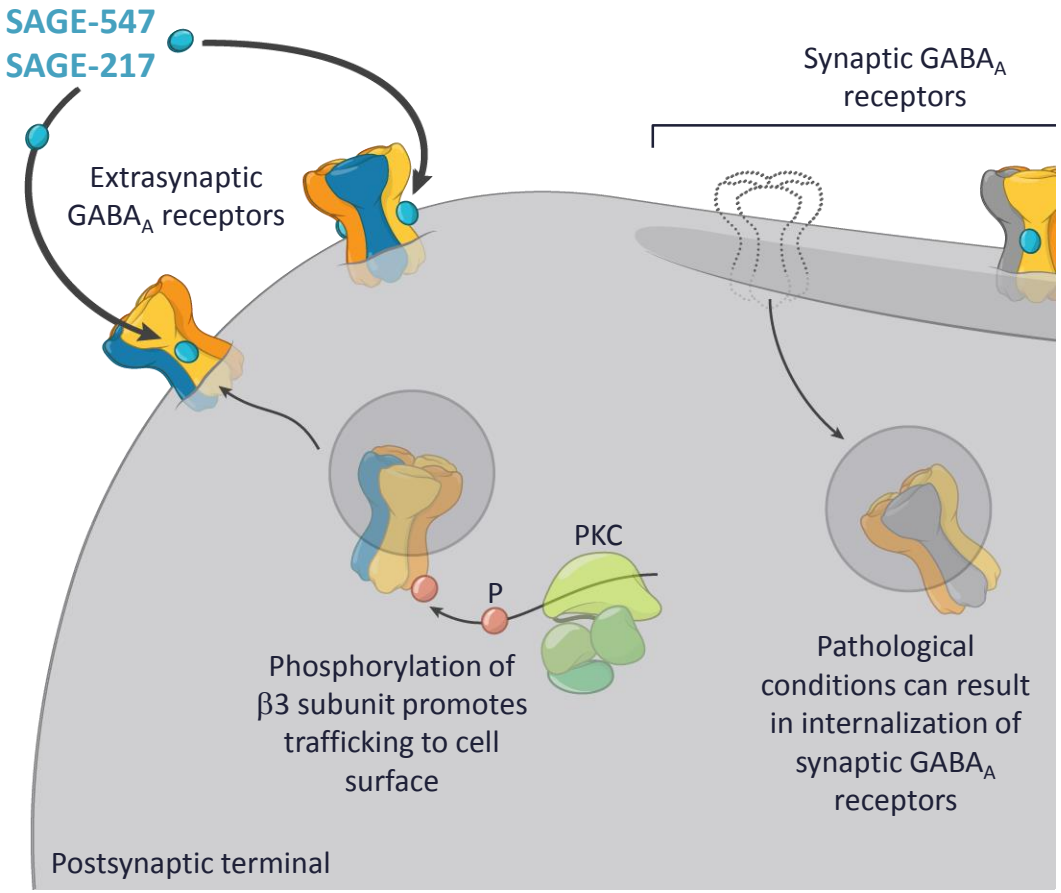
Acute Activity in PTZ Seizure Model[1]



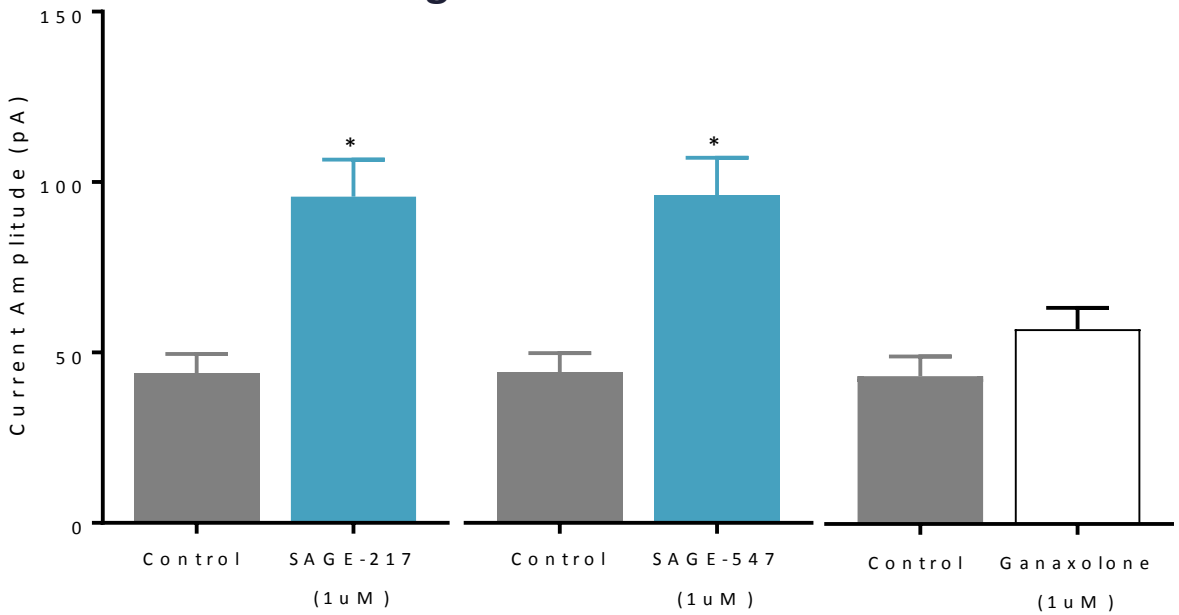
1. Hammond et al, Society for Neuroscience, 2015.

Certain Sage NAS Increase Surface Levels of Extrasynaptic $GABA_A$ Receptors in Animals

- Novel mechanism may contribute to the activity of SAGE-547 and SAGE-217
- Further exploring this metabotropic mechanism in animal models



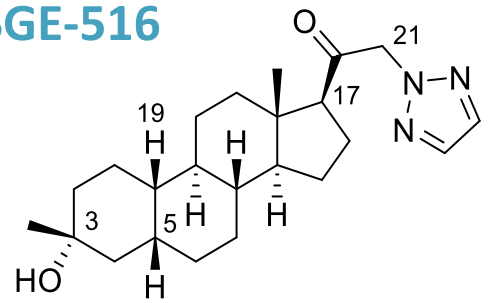
Certain Sage Compounds Induce a Prolonged Increase in Tonic Current

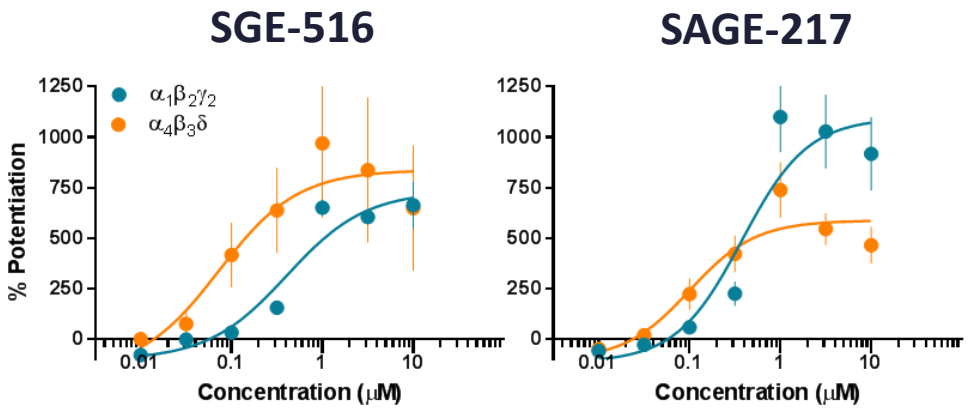


Source: Modgil et al, *Neuropharmacology*, 2016. Abbreviation: PKC, protein kinase C

Sage GABA Compounds Open a Broad Development Opportunity in a Spectrum of Diseases

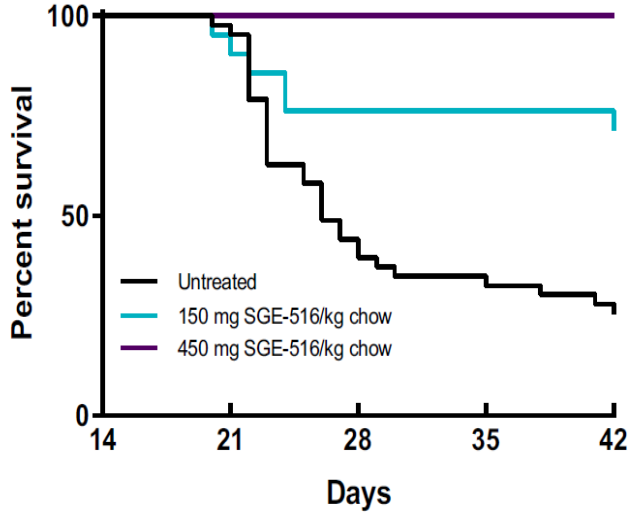
SGE-516





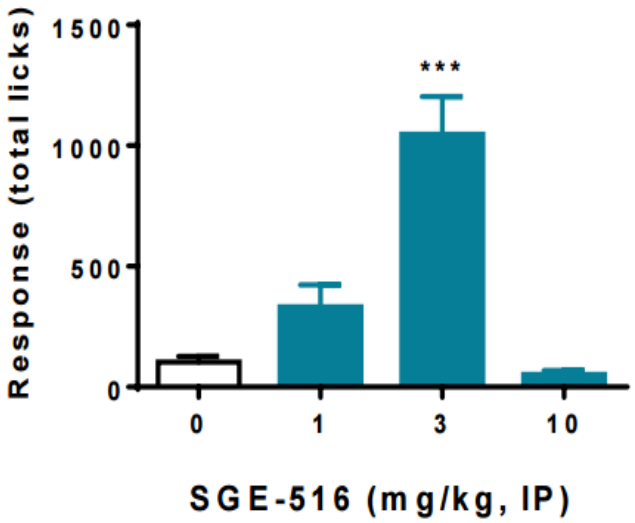
Key Sage tool compound for PoC and therapeutic utility

Prolonged survival in the *Scn1a+/-* Dravet mouse model[1]



- Orphan Epilepsies
- Pharmacoresistant GABAergic indications

Produced anxiolytic-like activity in Vogel Conflict Test model[2]



- Mood disorders
- Anxiety disorders
- Sleep disorders

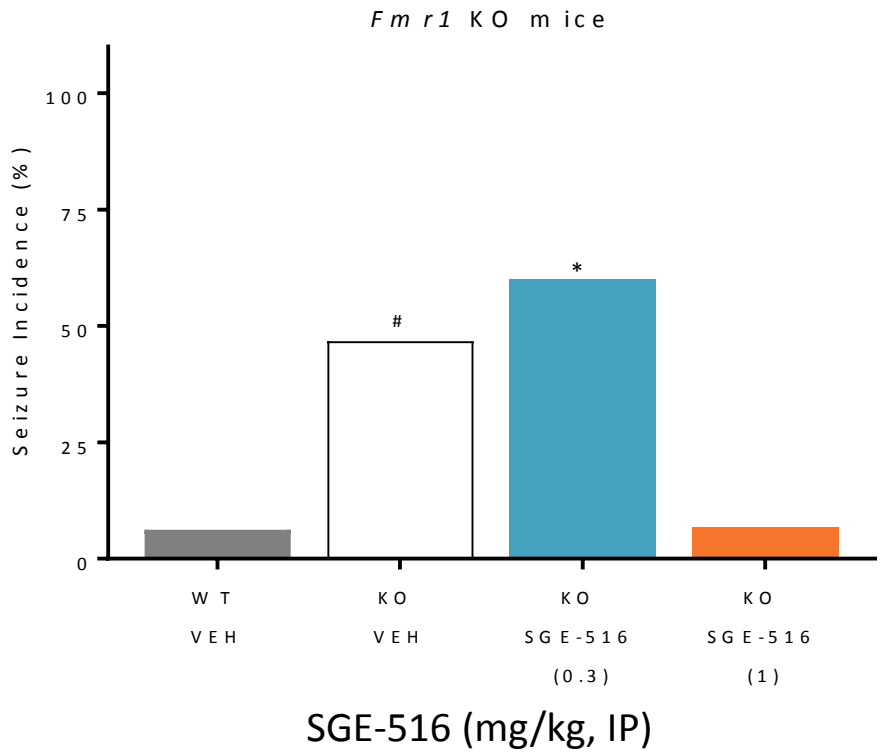
1. Hawkins et al, American Epilepsy Society Annual Meeting, 2016; 2. Hammond et al, Society for Neuroscience Annual Meeting, 2015.

NAS Effects in Mood Disorders – Autism Spectrum

Robust Protection from Audiogenic Seizures and Reversal of Spine Length Phenotype in Preclinical Models

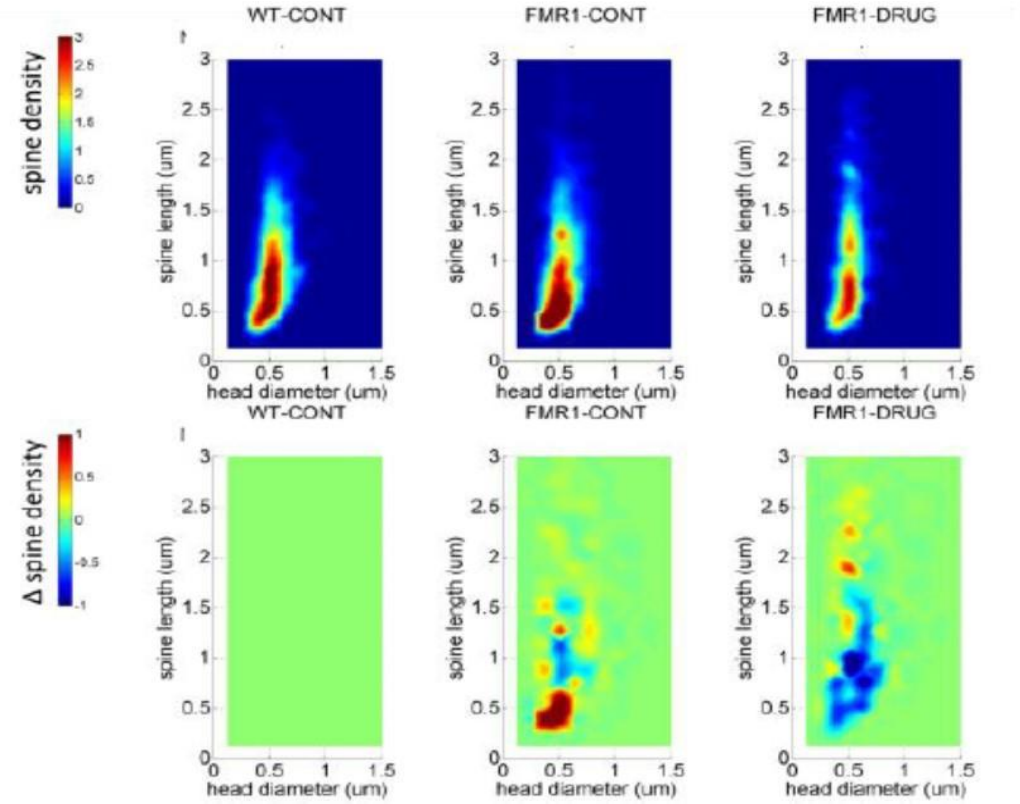
Autism Spectrum Disorders; Fragile X Syndrome

SGE-516 (acute) reverses susceptibility to seizure in *Fmr1* KO mice



Impact on disease progression in preclinical model

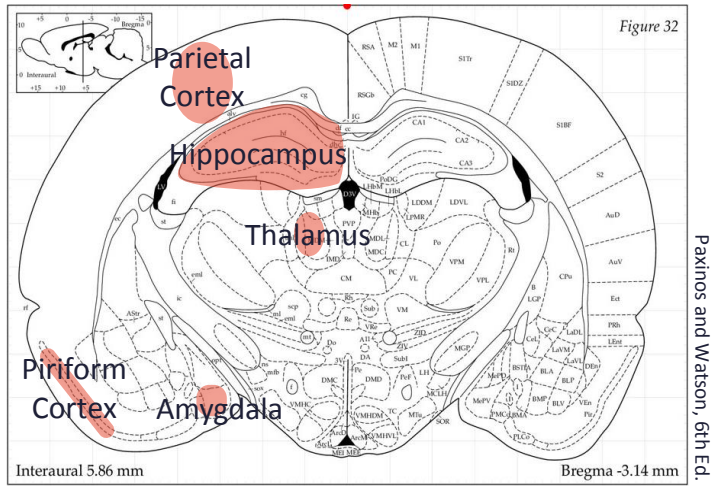
SGE-516 (chronic, 1 mg/kg equiv*) attenuates dendritic spine length phenotypes observed in *Fmr1* KO mice



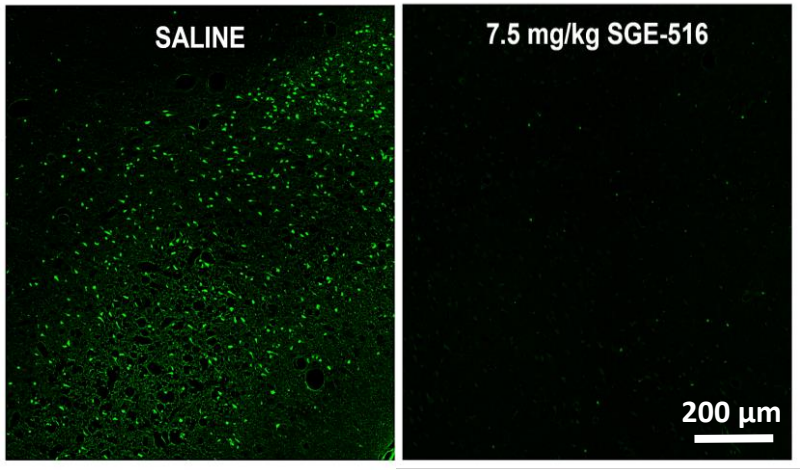
NAS GABA Modulators are Neuroprotective in Animal Models

SGE-516 Protects Against Cell Death Following Status Epilepticus in Animals

Brain regions

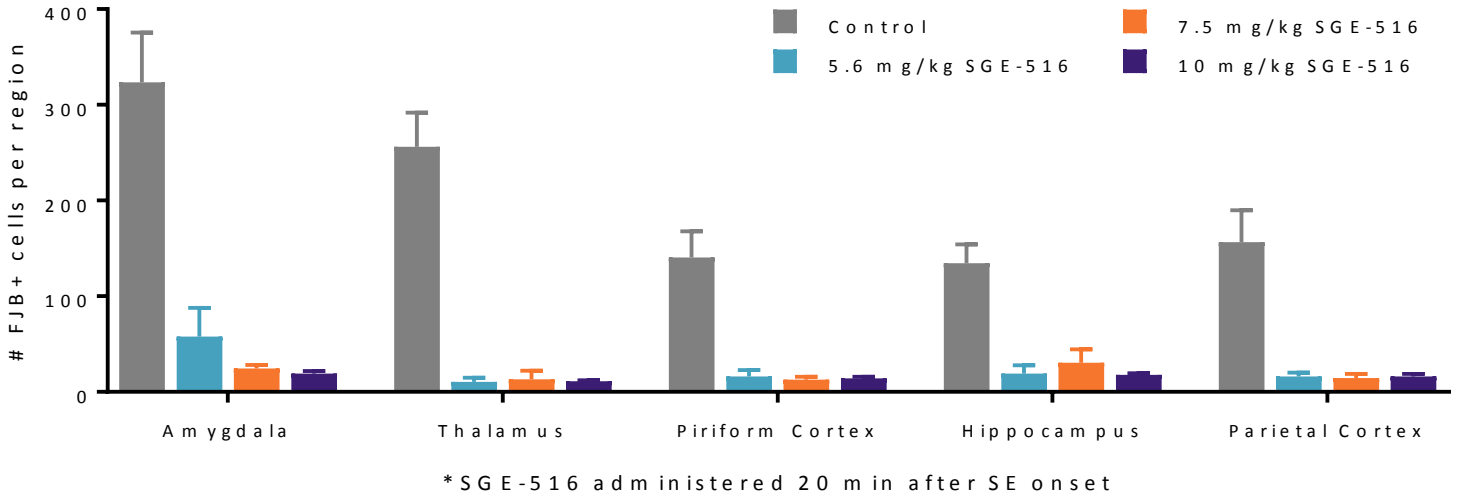


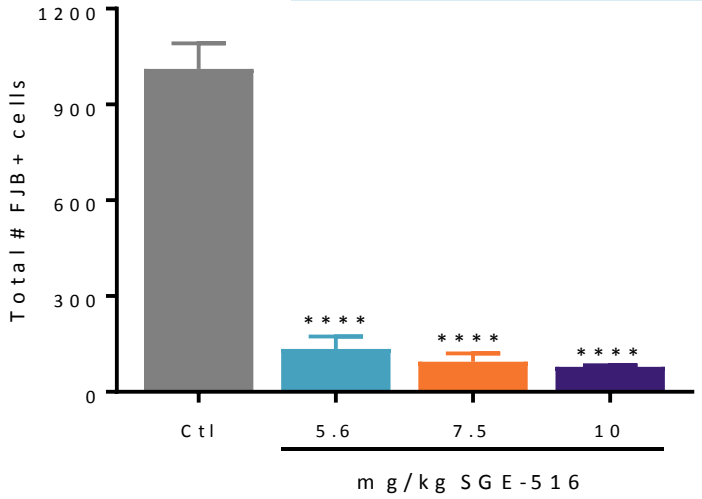
Sample images from the amygdala, FJB+ cells are green



Potential Utility of NAS:

- Neurodegenerative disorders
  - Parkinson's disease
  - Alzheimer's disease
  - Huntington's disease
- Neuroprotection
  - Stroke
  - TBI





Source; Althaus et al, American Epilepsy Society Annual Meeting, 2016.

…How?

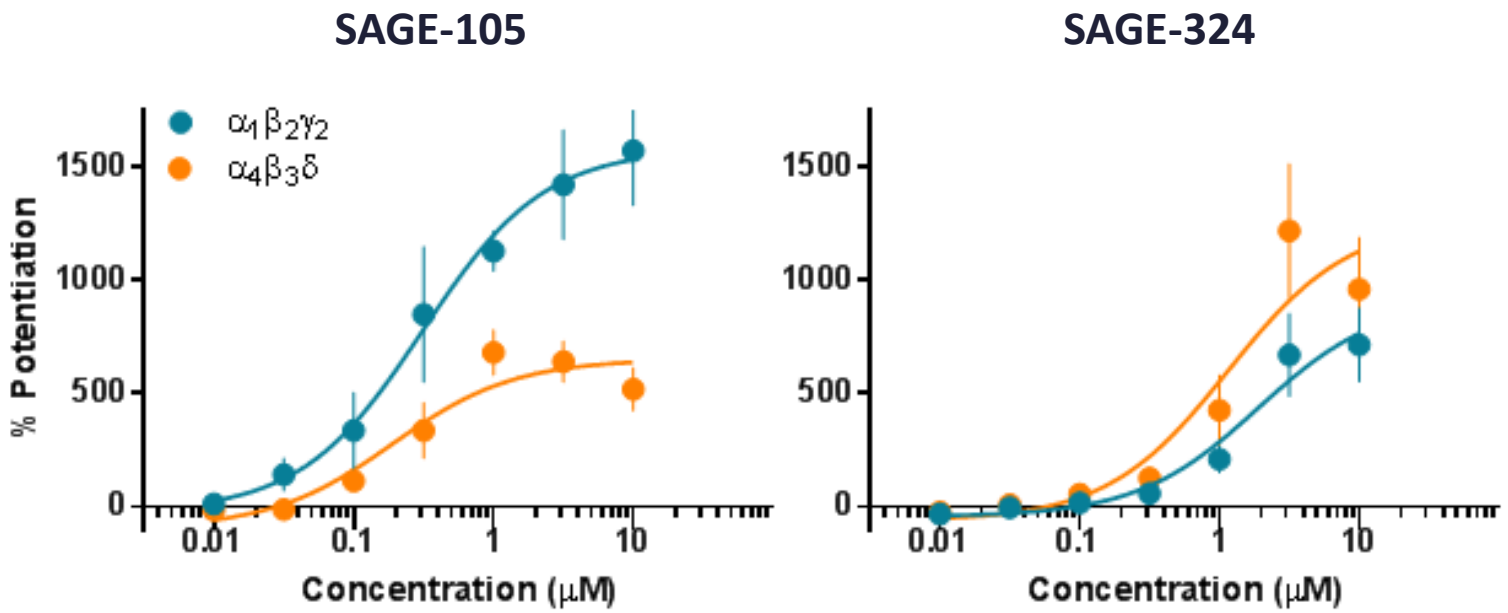
Equity in Hand to Expand Therapeutic Indications

Differentiated Next Generation Oral Programs

Pan-Selective Oral Modulators

- Robust preclinical efficacy
- Differentiated oral PK profiles
  - Structurally divergent
- Improved therapeutic index
- Potential for broad IP protection of NCEs

Advancing development candidates to clinical development

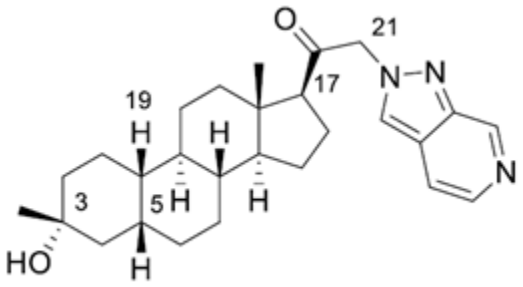


The Significant Potential of GABA

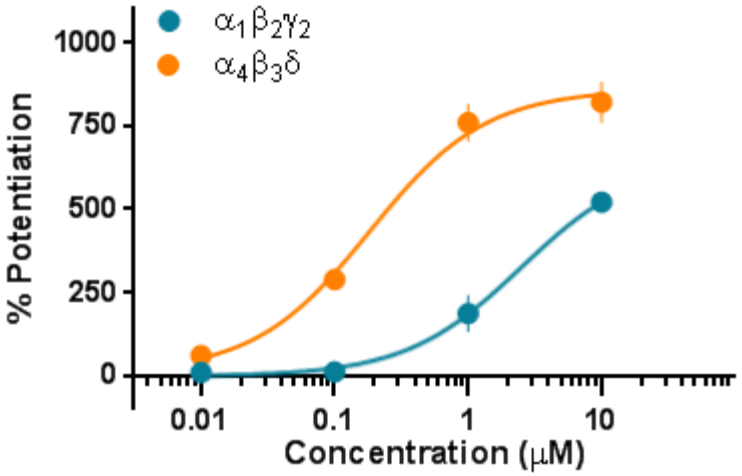
Novel Subunit-Selective Oral Modulators

Extrasynaptic-Selective Oral Modulators

- First to design subunit-selective $GABA_A$ receptor modulators
- Selective targeting of δ-containing receptors to enhance tonic GABAergic inhibition
- Targeting disorders associated with dysfunction of tonic GABA inhibition:
  - *Angelman's syndrome*
  - *Wilson's disease*
  - *Fragile X syndrome*
  - *Autism spectrum disorders*
  - *Anxiety disorders*
  - *Sleep disorders*



SGE-872

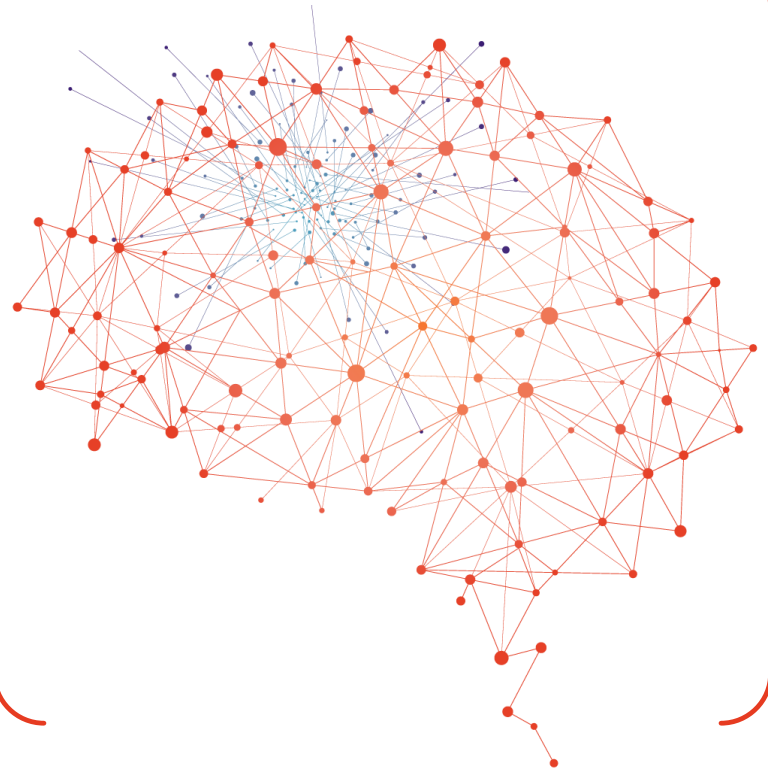


Source: Martin et al, *Journal of Neuroscience Research*, 2015.

SAGE THERAPEUTICS

GABA has Broad Therapeutic Potential

- Status Epilepticus
- SRSE
- Epilepsy
- Fragile X Syndrome
- Anxiety
- Postpartum depression
- Major depression
- Bipolar disorder

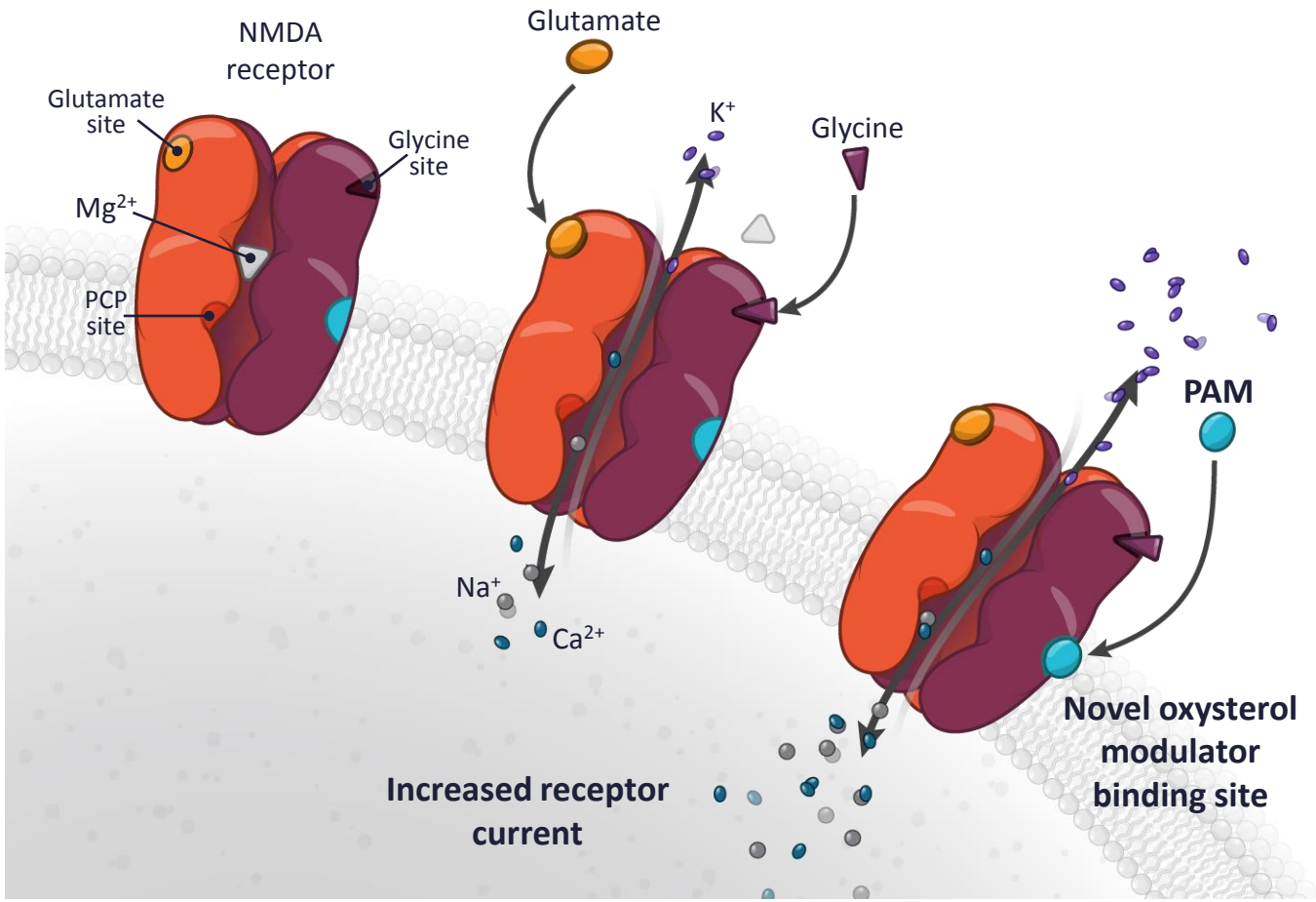


- Panic disorder
- Migraine
- Sleep
- Auditory
- Essential tremor
- Parkinson's disease
- Cognition
- Neurodegeneration

…Why NMDA Modulators?

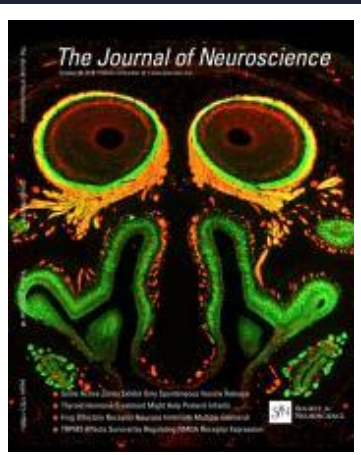
NMDA is a Key Regulator of Excitatory Neurotransmission

- NMDA plays a critical role in brain plasticity and neuronal network stabilization
- Loss of NMDA function may have significant impact on neuropsych disorders
- Existing NMDA agonists/antagonists have faced side effects and excitotoxity
- Sage has discovered a novel endogenous oxysterol-based modulatory mechanism
  - Potential for greater selectivity and minimal off-target effects

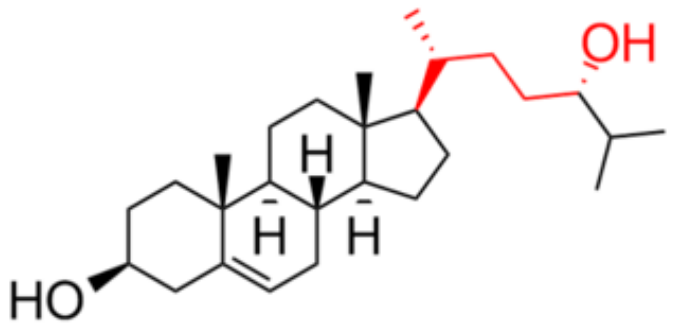


Sage Discovery

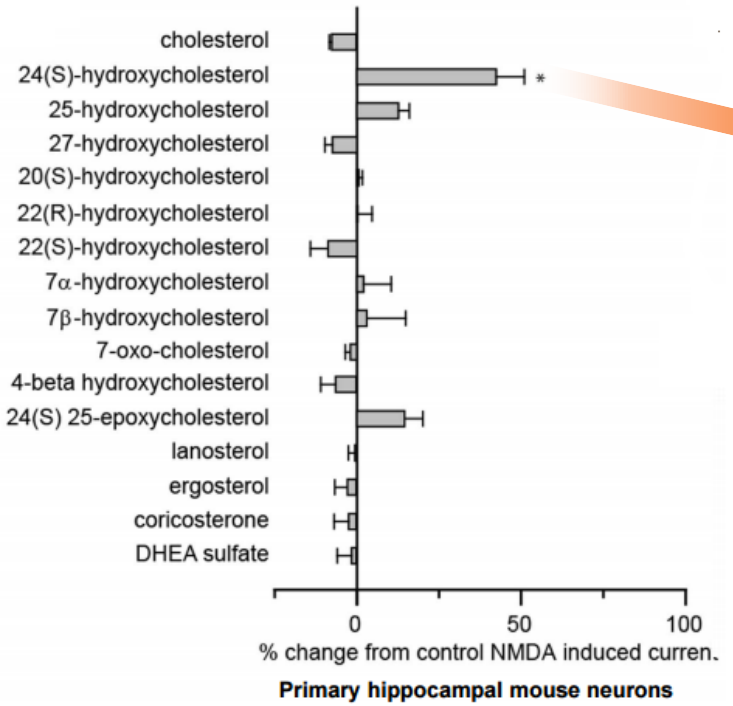
Endogenous Oxysterol-Based PAM of the NMDA Receptor

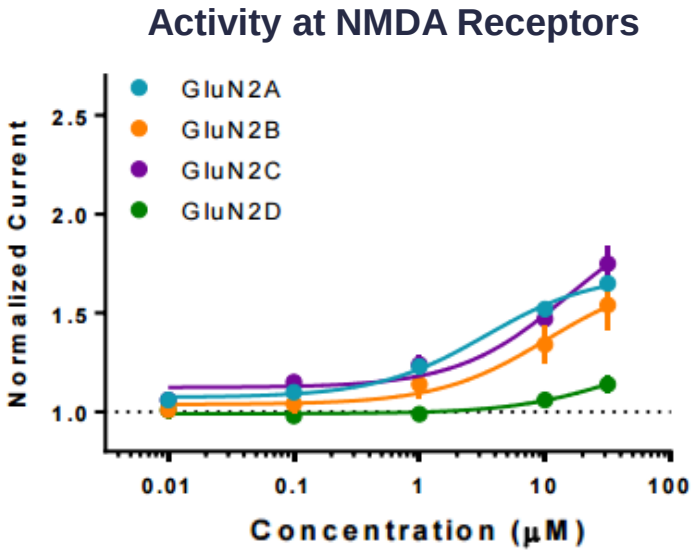


- 24S-HC is the major brain metabolite of cholesterol and is a potent endogenous PAM of the NMDA receptor
- Novel oxysterol-based NMDA PAMs may have broad utility for NMDA hypofunction disorders



24(S)-hydroxycholesterol





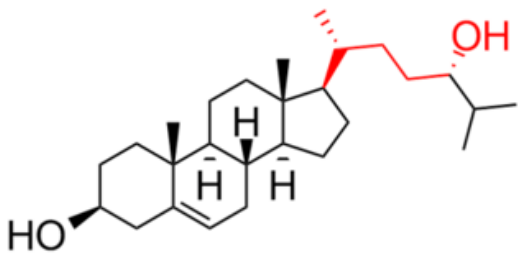
Source: Paul et al. *J. Neurosci*. 2013.

Leading NMDA Discovery Capabilities

Differentiated Allosteric Modulation, PK/PD Profiles and NMDA Receptor Selectivity

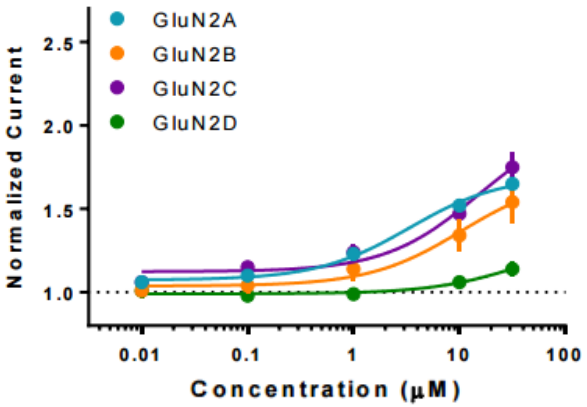
24S-HC

Structure



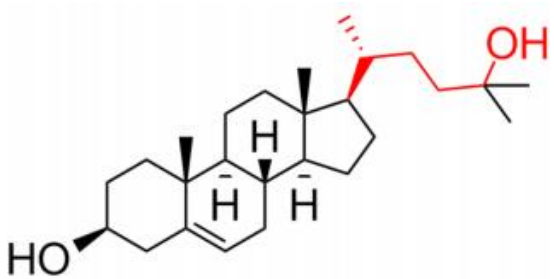
24(S)-hydroxycholesterol

Activity at NMDA Receptors



Sage Novel NMDA PAMs

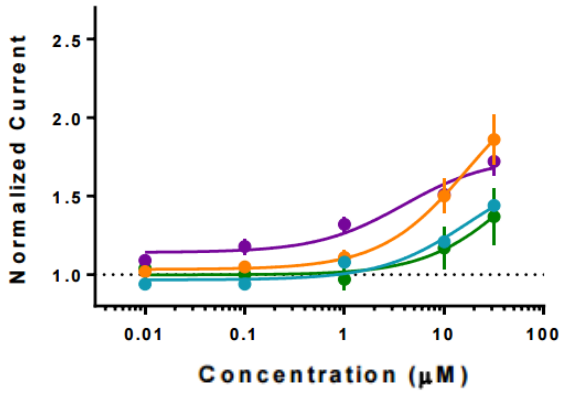
Structure



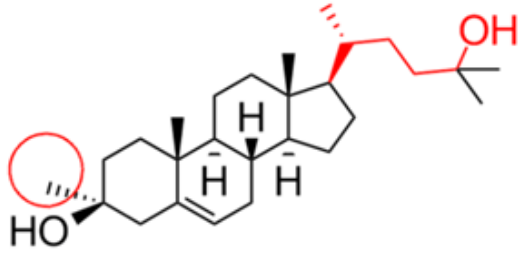
SGE-201

Activity at NMDA Receptors

SGE-201



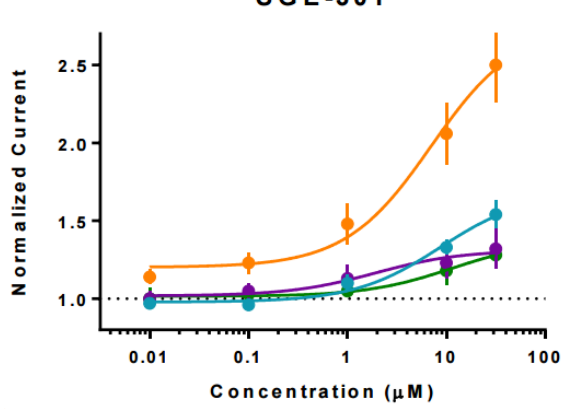
Structure



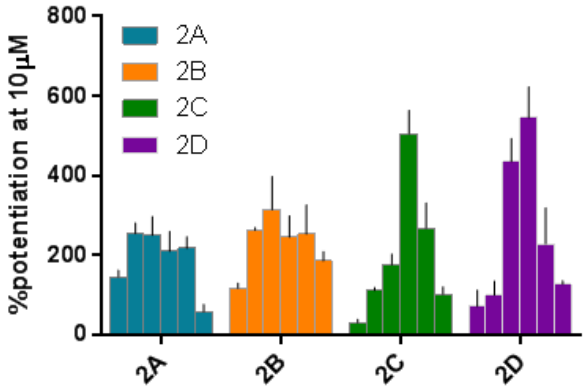
SGE-301

Activity at NMDA Receptors

SGE-301

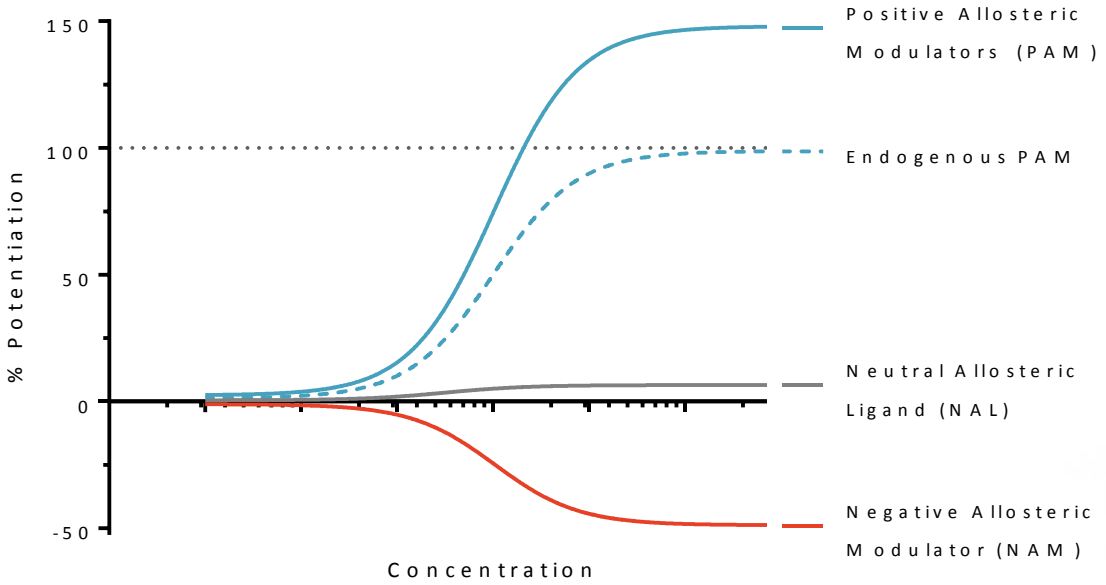


Diverse Subunit Selectivity (GluN2x)

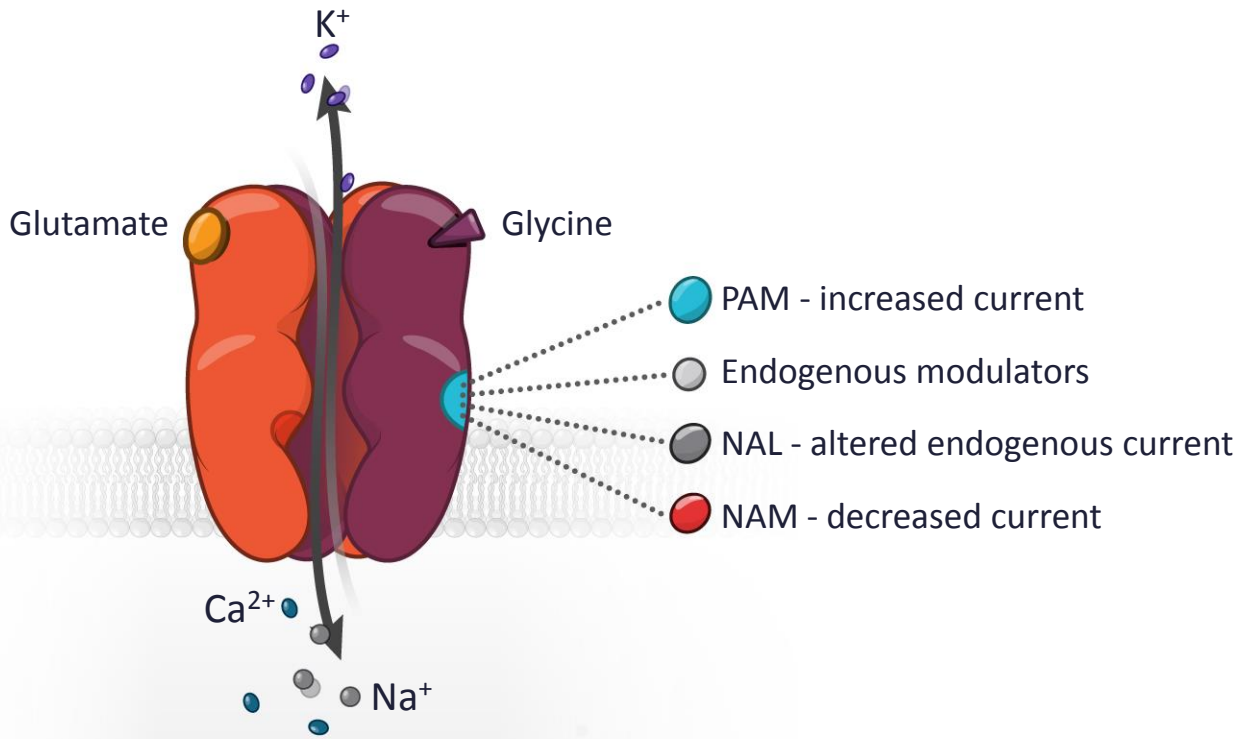


Sage has Created a Diverse NMDA NCE Library

Broad Spectrum of Allosteric Modulatory Mechanisms



Modulation	Therapeutic Potential
PAM	Cognition, NMDA Hypofunction
NAL	Depression, mood disorders
NAM	Treatment-resistant depression

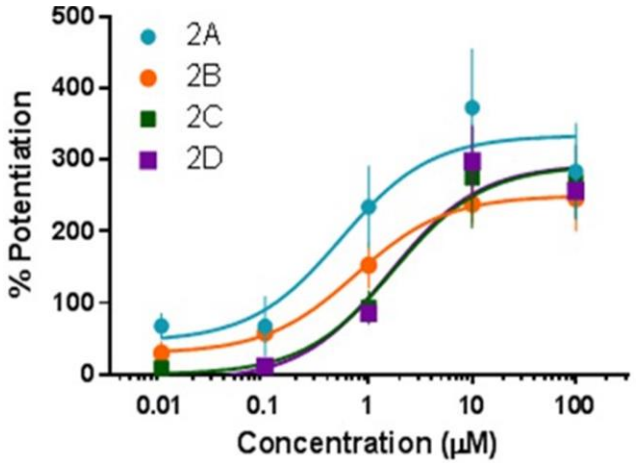


SAGE-718: Developing as a First-in-Class NMDA Modulator

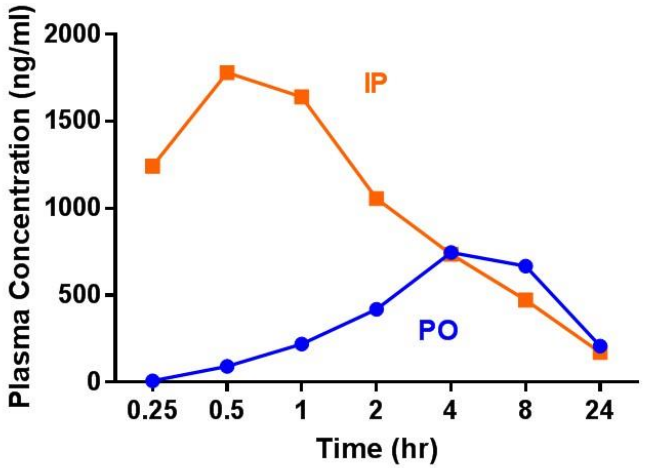
Expect to Begin Phase 1 Clinical Development in 1H 2017

- Potent and selective oxysterol-based NMDA PAM
- Good oral pharmacokinetic profile in animal models
- No off-target effects in a panel of 81 receptors and ion channels
- 24S-HC may serve as a peripheral biomarker for development

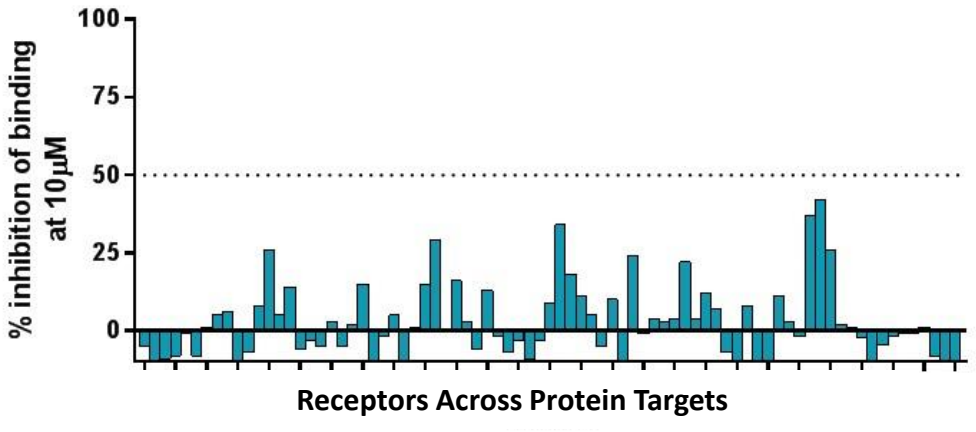
SAGE-718 Activity at NMDA Receptors (*in vitro*)



SAGE-718 Plasma PK (*in vivo*)



SAGE-718 Minimal Off-Target Activity (*in vitro*)

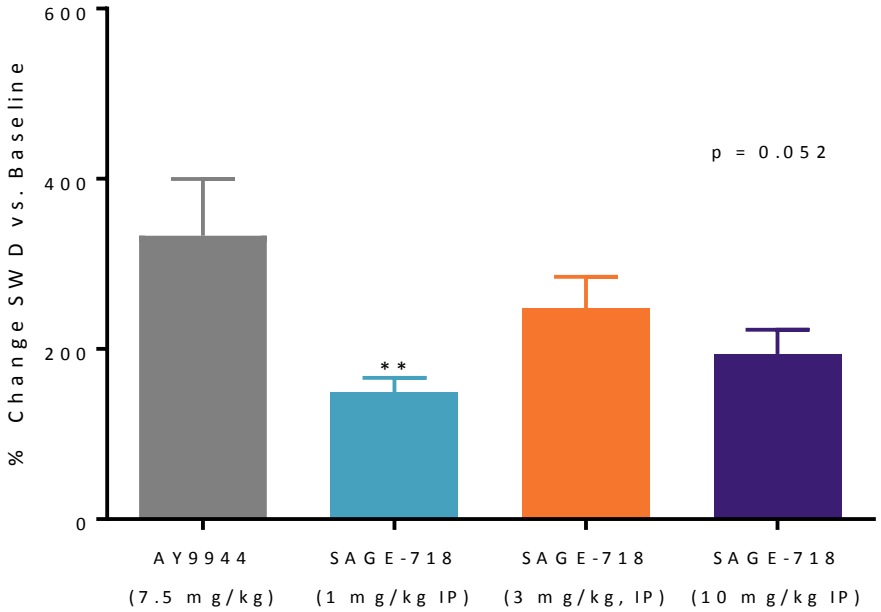


Source: Lewis et al, Society of Biological Psychiatry Annual Meeting, 2016.

Sage NMDA Compounds Open a Broad Development Opportunity in a Spectrum of Diseases

SAGE-718

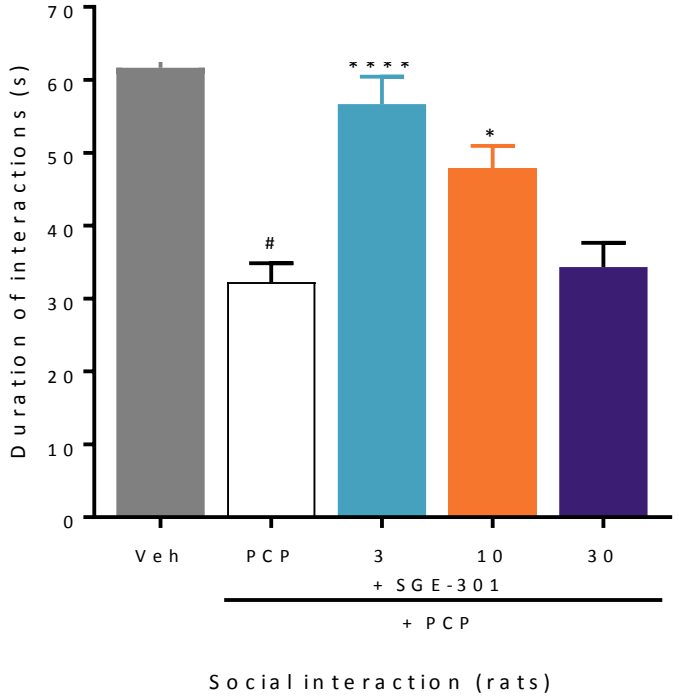
Reduced electrophysiological deficits in animal model of 24S-HC deficits[1]



- Smith-Lemli-Opitz Syndrome
- Huntington's
- Parkinson's Psychosis

SGE-301

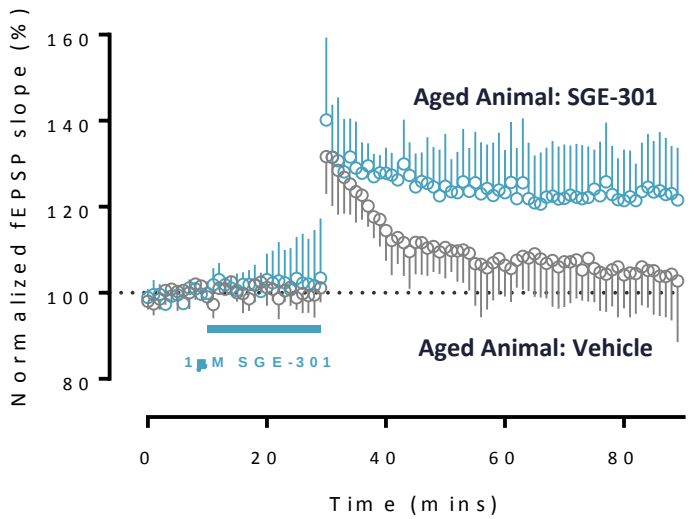
Active in sub-chronic PCP model of Schizophrenia[1]



- Cognitive Impairment associated with Schizophrenia

SGE-201

Enhances synaptic plasticity in aged rats



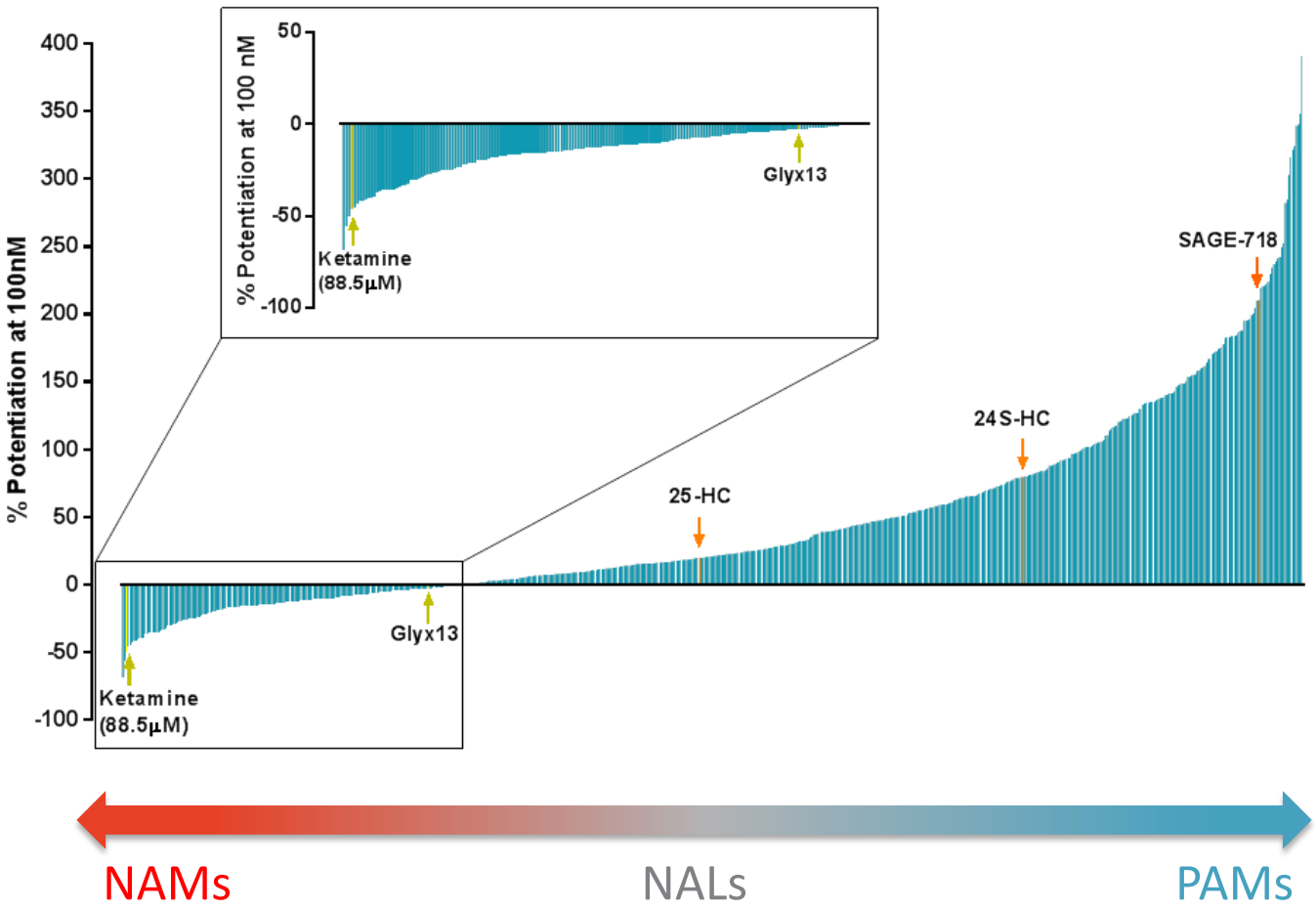
- Dementia
- Alzheimer's

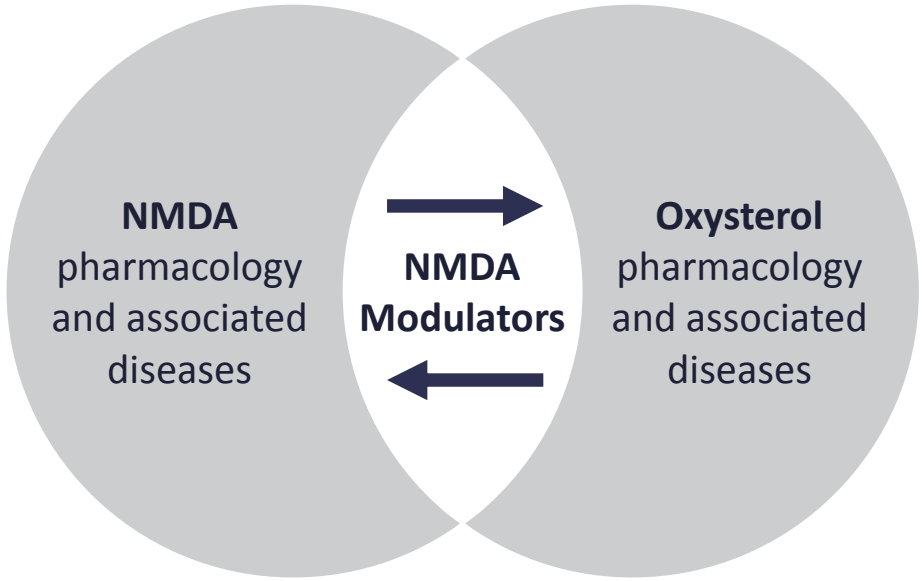
1. Lewis et al, Society for Neuroscience Annual Meeting, 2016; 2. Lewis et al, Society of Biological Psychiatry Annual Meeting, 2016.

Sage's Robust NMDA Chemical Library

Over 800 Compounds with Broad Therapeutic Potential

Designed for Purpose Compound Library





- Anti-NMDA Receptor Encephalitis
- Schizophrenia
- Depression
- Mood disorders
- Cognition
- Dementia
- Cerebrosterol Deficit Disorders
- Autism Spectrum Disorders
- Huntington's

Sage is Focused on Innovating Novel CNS Compounds

Powerful Mechanisms

- Modulation of key regulatory brain networks by Sage compounds has the potential to provide differentiated approach in numerous CNS disorders

Innovation

- Sage's novel compounds have demonstrated broad activity across preclinical and clinical studies

Speed

- Discovery capabilities and preclinical validation capable of rapidly progressing diverse NCEs with first-in-class potential to the clinic

SAGE THERAPEUTICS™

Translational Neuroscience

Jim Doherty, PhD – SVP, Research

Sage's Approach to Translational Neuroscience

Increasing the Probability of Technical Success in Drug Development

Do we have the right dose?

- How much drug needs to get into the brain?
- How long does the drug need to remain in the brain?
- Are we modulating the right circuits?

Are we treating the right patients?

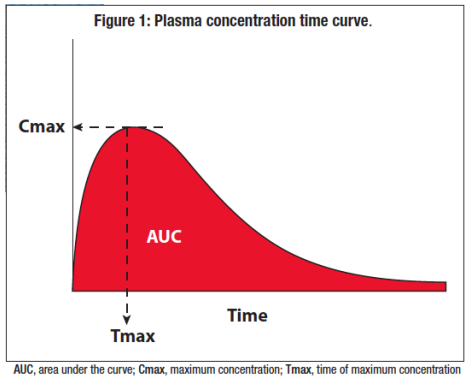
- Which patients will respond best to the drug?

- Identify **functional biomarkers** in animals that respond to **target engagement** and can be deployed in human clinical trials
- Identify **genetic and biochemical** criteria to identify **patient populations** to increase the technical chances of success of a clinical trial
- Translate insights **between compounds** and **indications** for better odds of success across pipeline

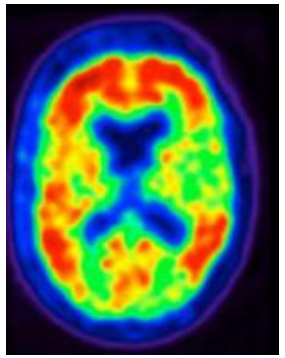
Translational Toolkit in CNS

- Objectives
  - Target engagement
  - Functional changes
  - Patient stratification
  - Disease susceptibility
  - Individual differences in response

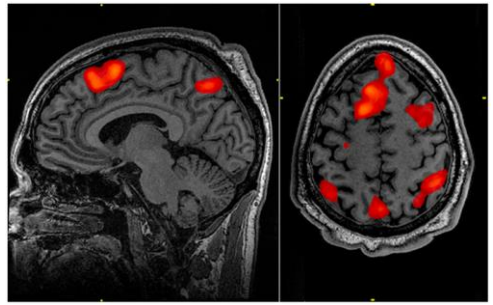
Peripheral



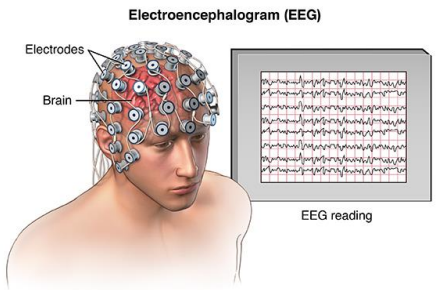
PET Imaging



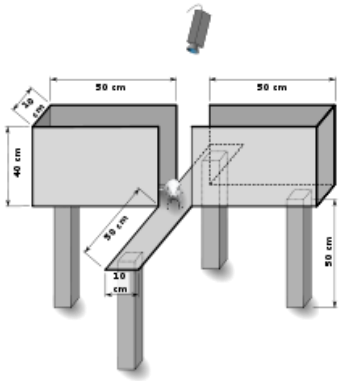
Functional Imaging



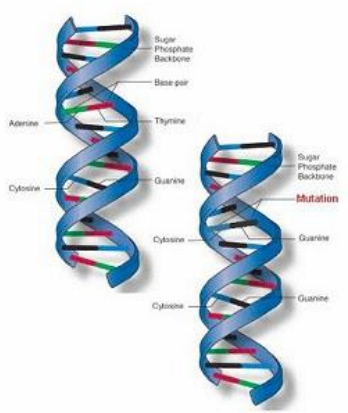
Electrophysiology



Behavioral

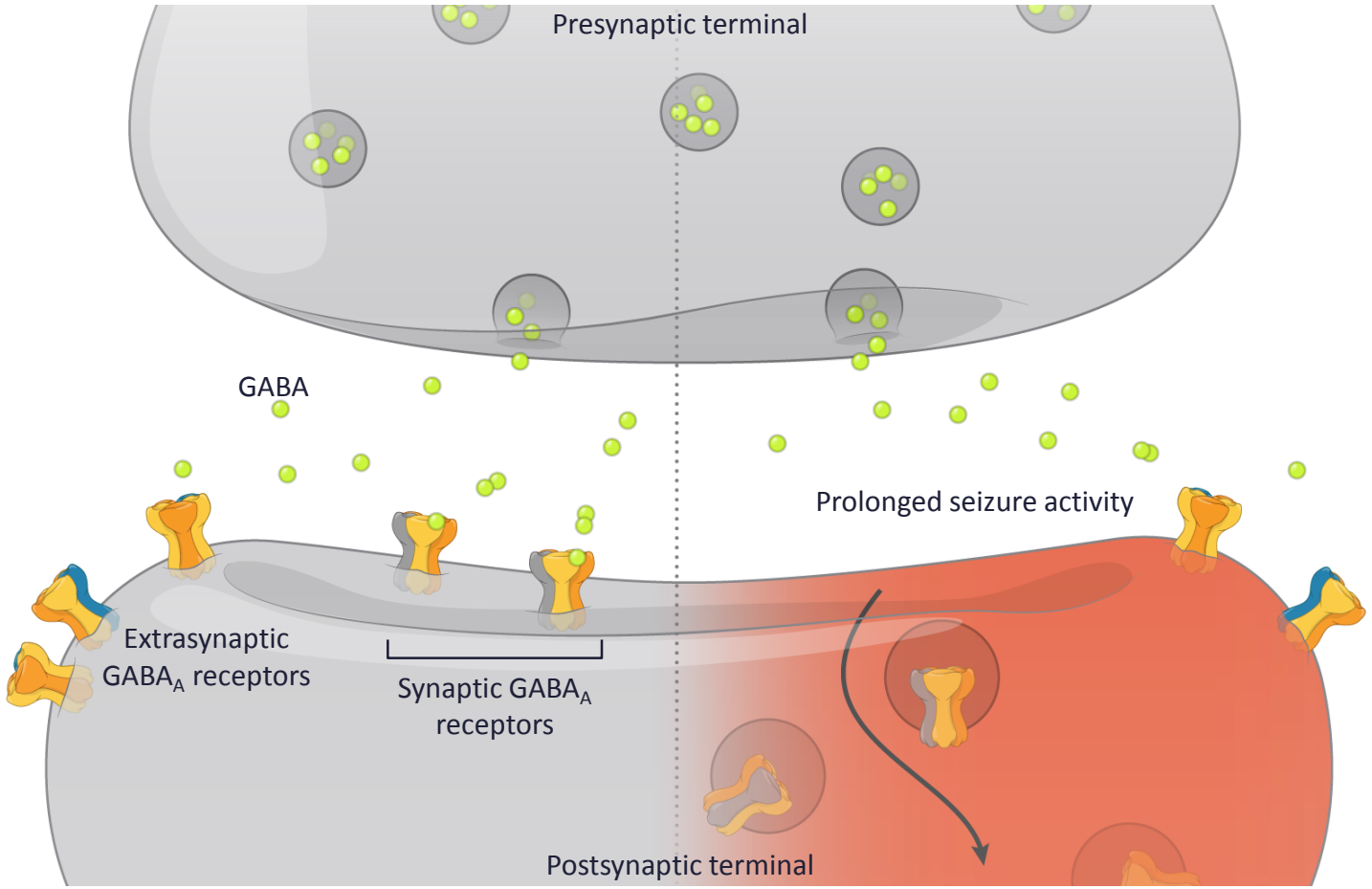


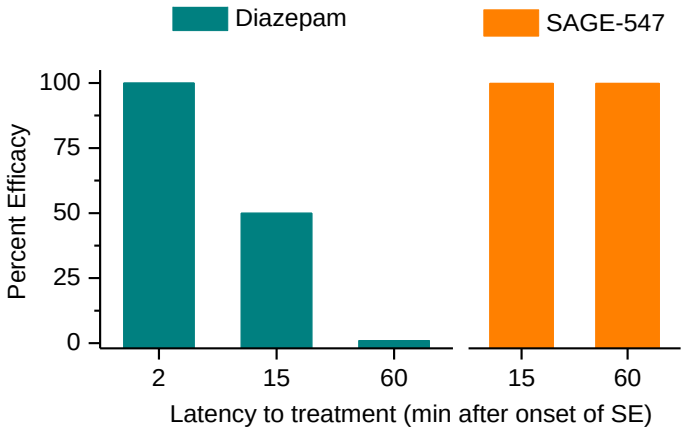
Genetics

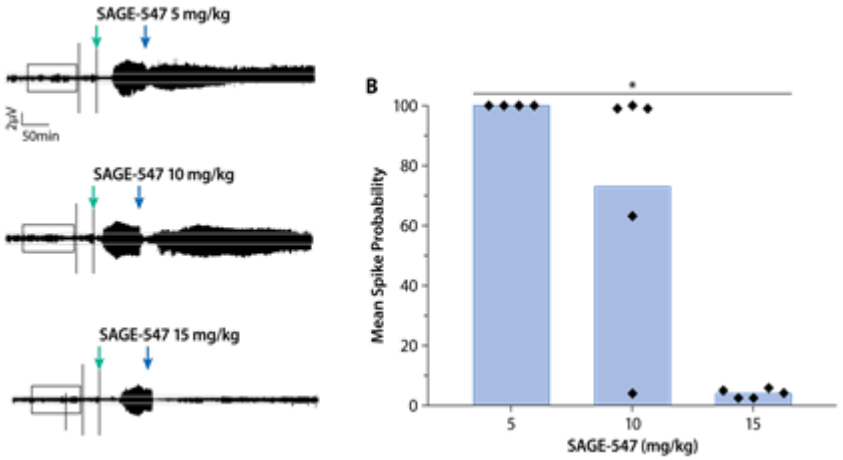


SAGE-547 Arrests Refractory SE in a Rodent Model

Inhibitory $GABA_A$ Receptors May Play an Important Role in SRSE





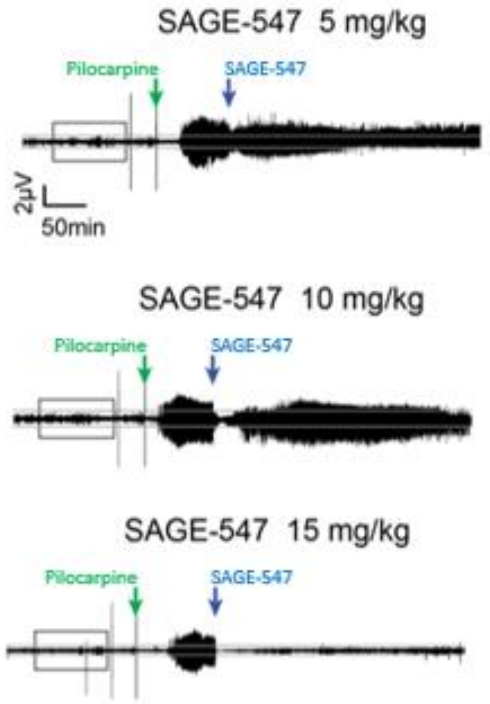


Status Epilepticus Models

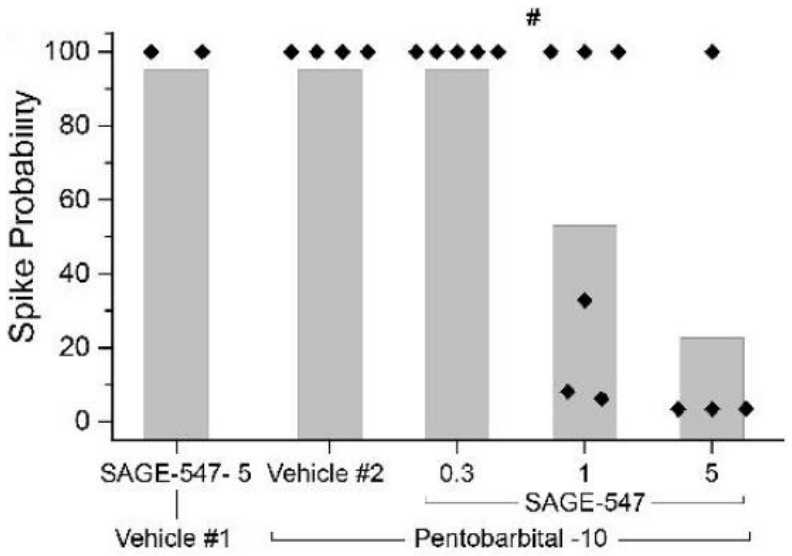
Translating Activity from Animals to Clinic for SAGE-547

SAGE-547 Preclinical

SAGE-547 Halts Pharmaco-Resistant RSE in Animals[1]

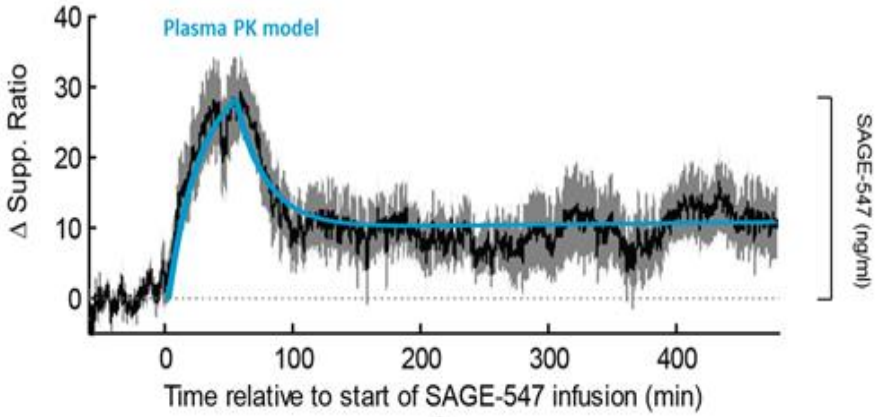


SAGE-547 Activity Enhanced by Pentobarbital in Rats[1]



SAGE-547 Phase 1/2

SAGE-547 Increased EEG Suppression of SRSE Patients Optimally Suppressed at Baseline[2]

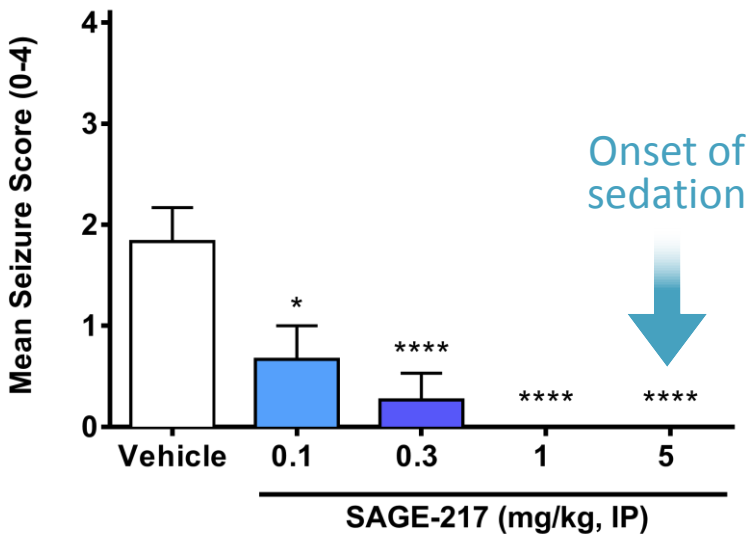


1. Ackley et al, Society for Neuroscience Annual Meeting, 2016; 2. Rosenthal et al, American Academy of Neurology Annual Meeting, 2015.

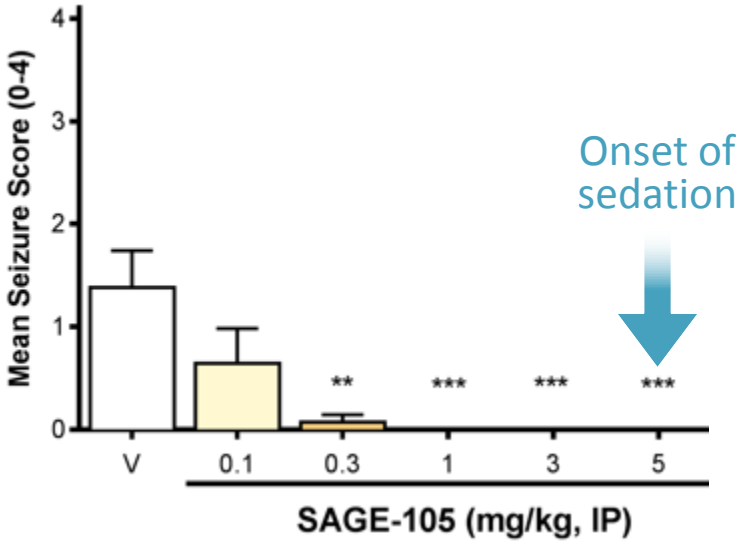
Seizure Models

Potent Activity Across Compounds with Wide Therapeutic Margin in Preclinical Models

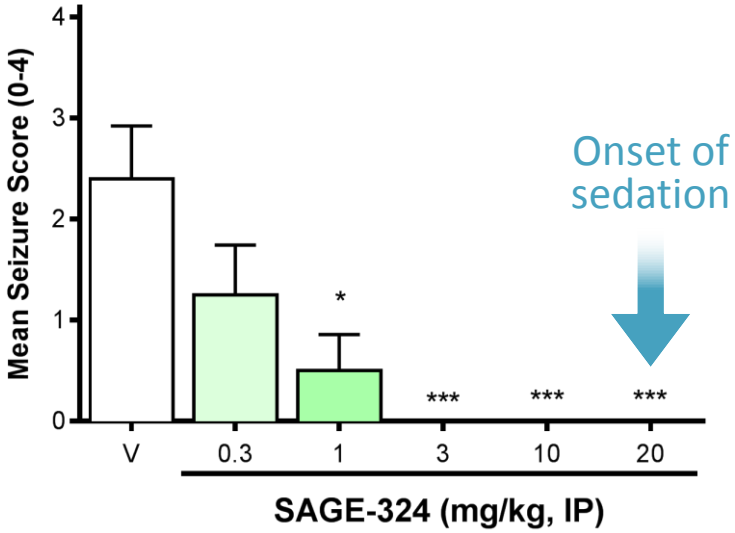
SAGE-217



SAGE-105



SAGE-324



- *Fmr1* Knockout Mouse Model of Fragile X Syndrome

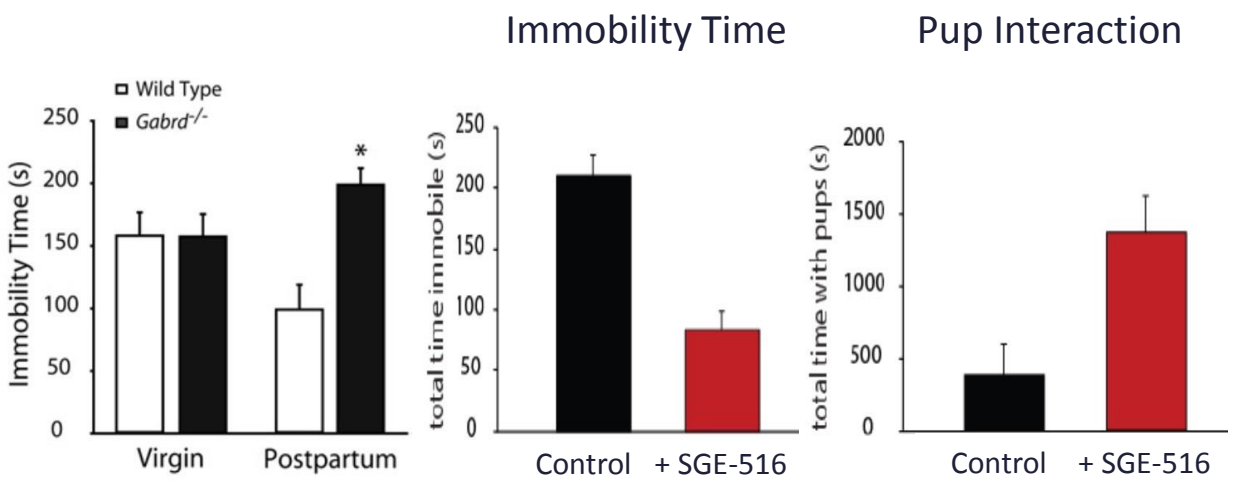
Source: Belfort et al, American Epilepsy Society Annual Meeting, 2016.

Mood Disorders

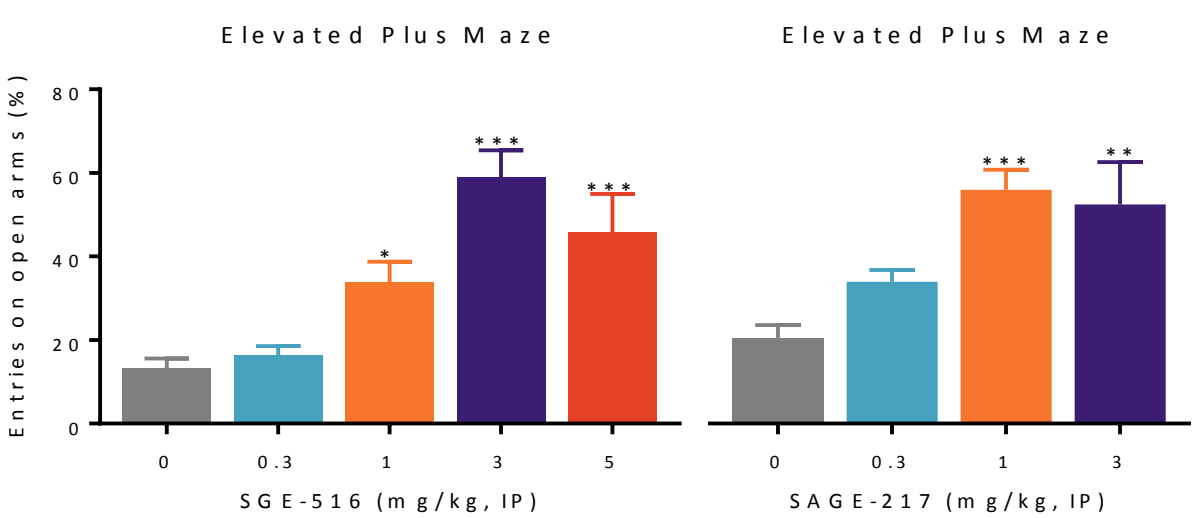
Extending SAGE-547 PPD Data through Biomarkers and Preclinical Research

- Using genetic risk factor and plasma biomarker data to evaluate other subgroups of mood and anxiety disorders for potential study
- SGE-516 significantly reduces PPD-like behaviors in mouse genetic models of PPD
- Sage GABA PAMs profile as anxiolytics in rodent models of anxiety

PPD-like Behaviors in GABA δ -/- Mice



Elevated Plus Maze Model of Anxiety



Source: Maguire J, Mody I, *Neuron*, 2008.

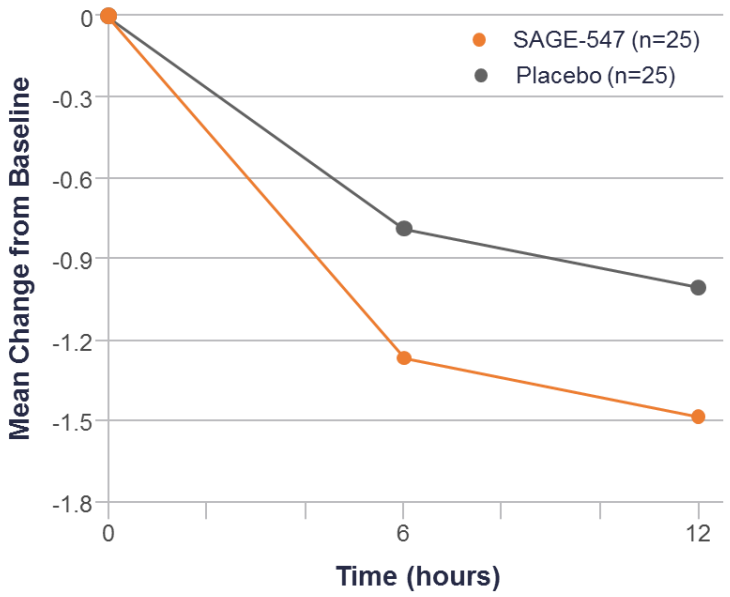
Movement Disorders

Anti-Tremor Activity Translates Across Sage Compounds

- Proof-of-concept data from SAGE-547 and SAGE-217 trials
- Clinical insights are being “back-translated” into animal models of movement disorders

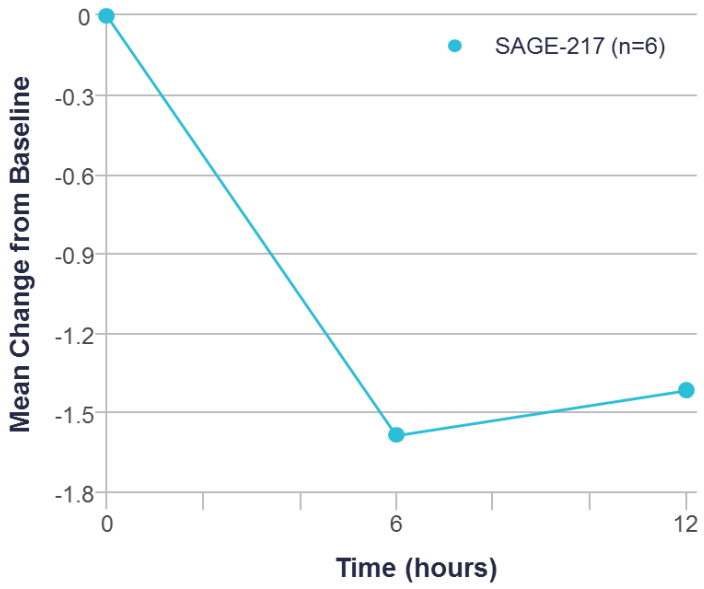
SAGE-547 Placebo-Controlled Probe Study

TETRAS Kinetic Tremor Score Change from Baseline



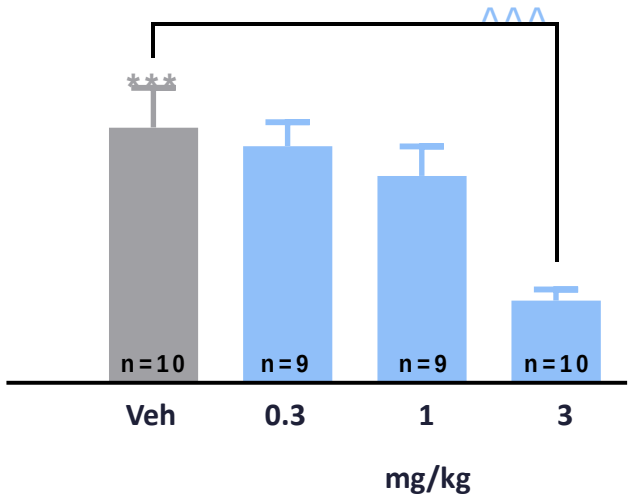
SAGE-217 Open-Label Phase 1 Cohort

TETRAS Kinetic Tremor Score Change from Baseline



SAGE-217 is Active in Preclinical Model

Reserpine-induced Dyskinesia



Movement Disorders

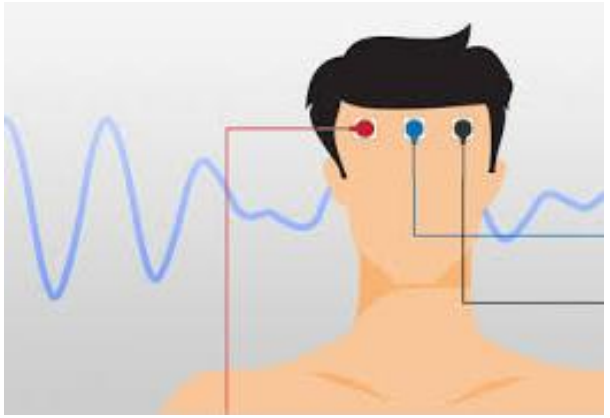
Leveraging Real World Data Collection

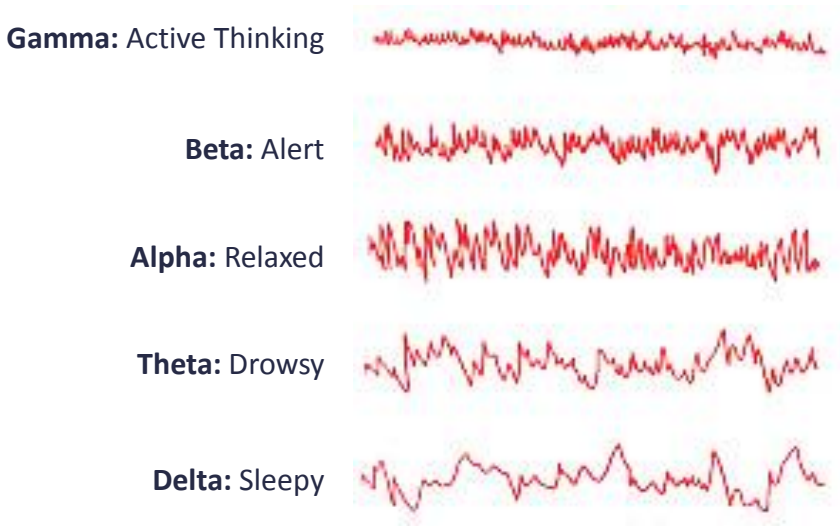
- Implementing continuous data collection into our movement disorder trials with the Empatica E4 wristband
- Device provides remote physiological monitoring for:
  - Tremor duration / amplitude (accelerometer)
  - Heart rate / BP
  - Stress response
  - Sleep profile
- Developing data analysis tools to integrate motor and behavioral state information
- Studies offer potential to correlate clinical and real world outcome measures

EEG as a Functional Biomarker for Dosing

Well-Established for CNS Target Engagement

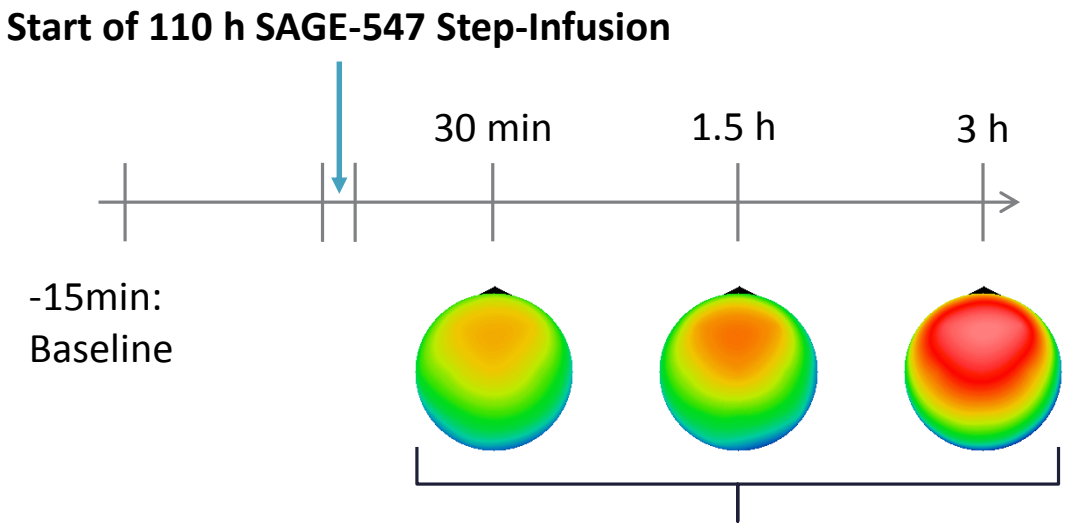
- EEG (electroencephalogram) is a passive measure of the combined activity of a large number of neurons
- Easy to collect; feasible for long recording sessions with millisecond time resolution
- GABA modulators produce a concentration dependent changes the power of EEG bands
- Sage measures increases in beta-band EEG (β-EEG) power as a functional biomarker in animals and humans



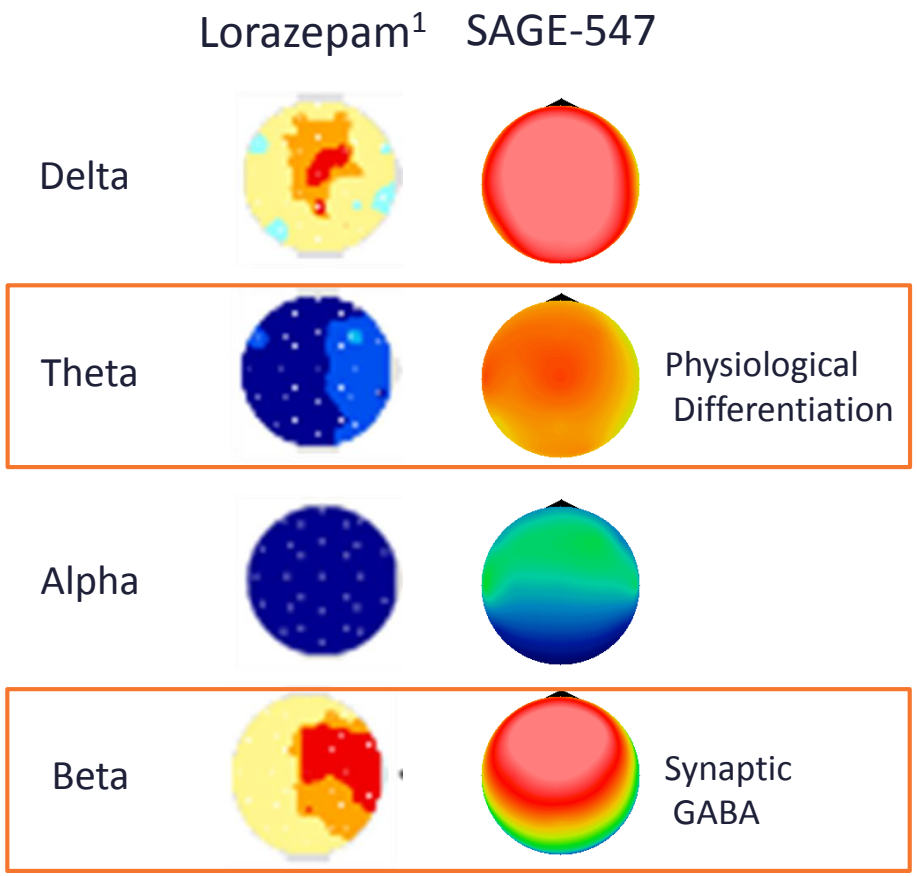


Demonstrating GABAergic Target Engagement on EEG

- Cortical EEG can provide a 'real-time' physiological readout of drug associated changes in brain dynamics
- EEG profile of SAGE-547 different from benzodiazepines
- At targeted therapeutic drug levels, SAGE-547 produces concentration dependent increase in beta-EEG



EEG 'Fingerprint'



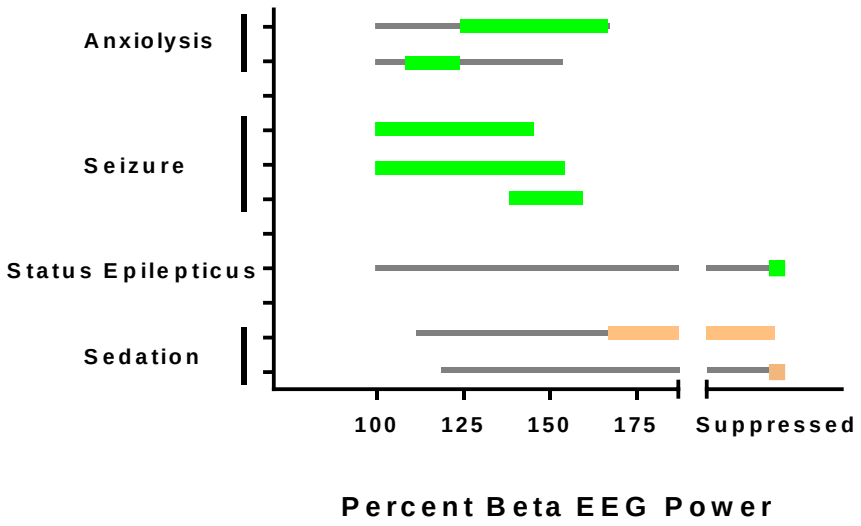
1. Adapted from Gilles et al, *Dialogues in Clinical Neuroscience*, 2002.

Functional Biomarkers Translate Between Compounds

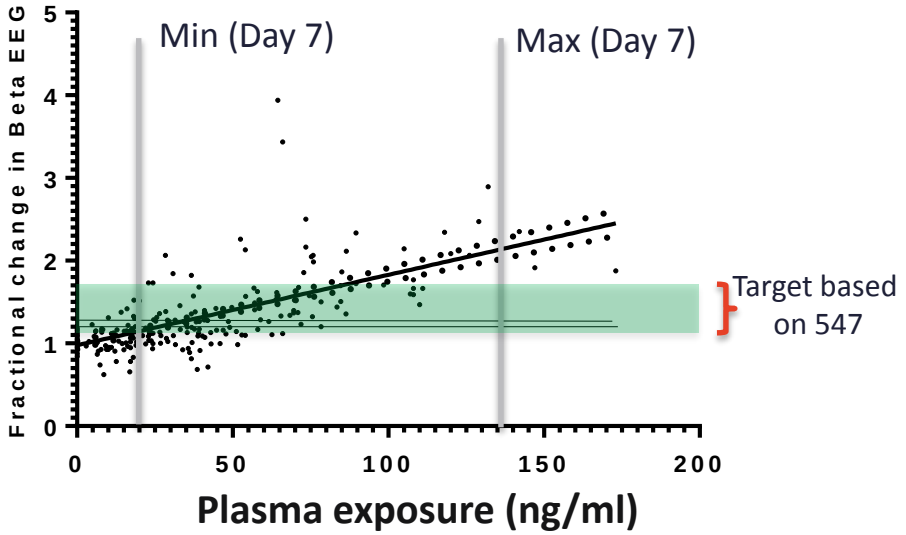
Beta-band EEG to Estimate SAGE-217 Dosing

- β-EEG used to translate dosing between SAGE-547 and SAGE-217
- SAGE-217 Phase 1 measured β-EEG power in humans to compare against activity in SAGE-547 human studies and SAGE-217 preclinical studies

SAGE-217 Preclinical



SAGE-217 Phase 1



$GABA_A$ Platform Target Validation

Strong Read-through Across Compounds and Indications

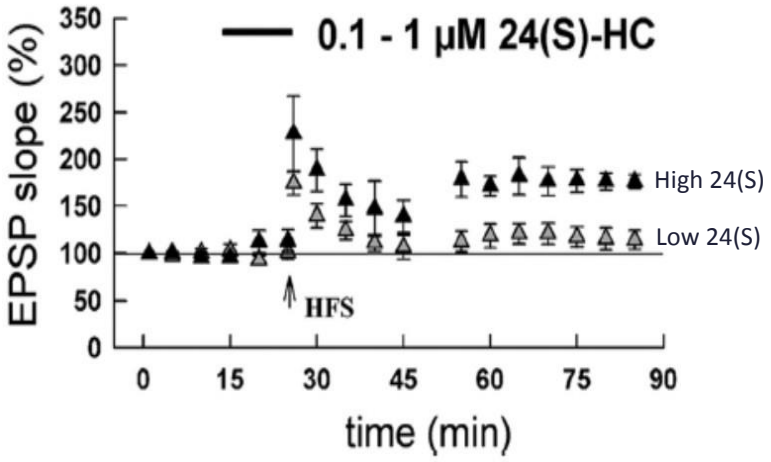
		Seizure Disorders	Mood Disorders	Movement Disorders	Functional Biomarker	$GABA_A$ Pharmacology
Clinical	SAGE-547	✓ SRSE	✓ PPD	✓ ET	✓ EEG Power	
	SAGE-217			✓ ET	✓ EEG Power	
Preclinical	SAGE-547	✓ RSE model	✓ Anxiety models		✓ EEG power	✓
	SAGE-217	✓ Multiple seizure models	✓ Anxiety models	✓ Dyskinesia model	✓ EEG power	✓
	SAGE-105	✓ Multiple seizure models	✓ Anxiety models		✓ EEG power	✓
	SAGE-324	✓ Multiple seizure models	✓ Anxiety models		✓ EEG power	✓
	SGE-516 (tool)	✓ Multiple seizure models	✓ Anxiety models	✓ Dyskinesia model	✓ EEG power	✓

SAGE THERAPEUTICS

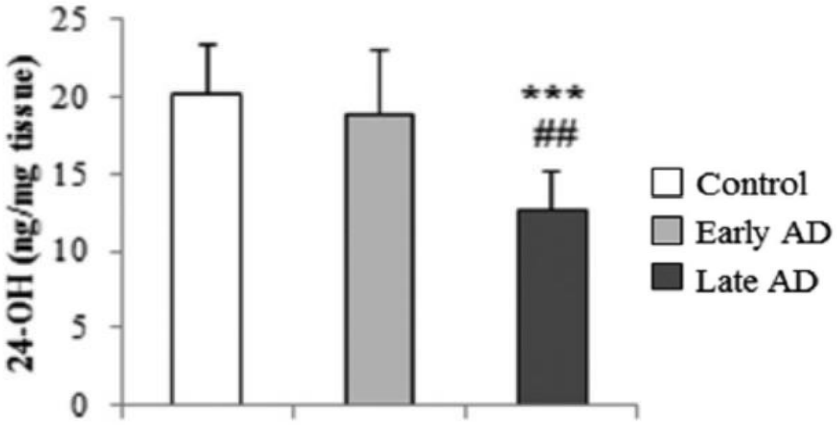
Synaptic Plasticity, 24S-HC and Cognition

In Vitro Models and Patient Biomarker Identification

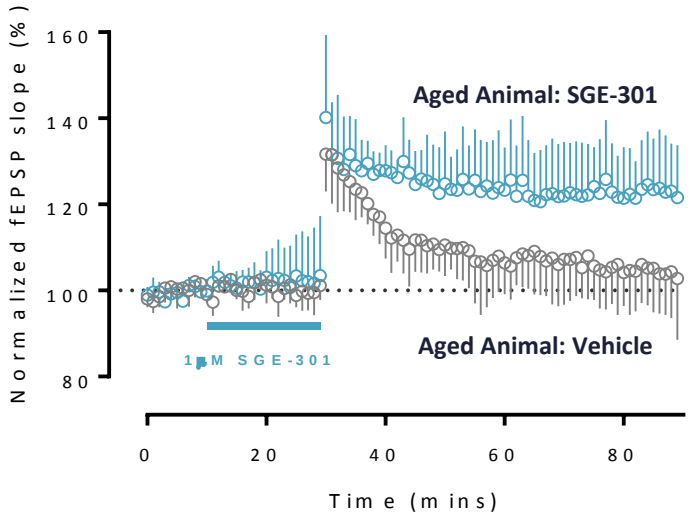
Levels of 24S-HC can influence the strength of synaptic plasticity[1]



Decreased 24S-HC has been documented in Alzheimer's disease[2]



Age related deficits in synaptic plasticity can be attenuated by SGE-301



- Building patient sample collection including Alzheimer's, Huntington's, Parkinson's Disease and Autism, all of which have documented changes in cognition
- Goal to identify populations with low levels of 24S-HC that may be sensitive to modulation of NMDA receptors

1. Paul et al, *Journal of Neuroscience*, 2013; 2. Testa et al, *Redox Biology*, 2016.

Which Patients May Benefit from Enhancing NMDA Function?

Identifying Biomarker-based Patient Subgroups with Clear Expansion Opportunities

Anti-NMDA Antibody Associated Disorders

- Initial patient population: Anti-NMDA Receptor Encephalitis (ANRE)
  - Acute, recurrent disorder(s)
  - Primarily CNS deficits
  - Adolescent and adult populations
  - Key CNS related abnormalities:
    - Cognitive and executive function deficits
    - Psychosis, agitation, aggression
    - Status epilepticus / seizures
    - Insomnia, movement disorders
  - EEG abnormalities: Extreme delta brush

- **Expansion indication:** Dementia with serum antibodies for NMDA (IgA/IgM)

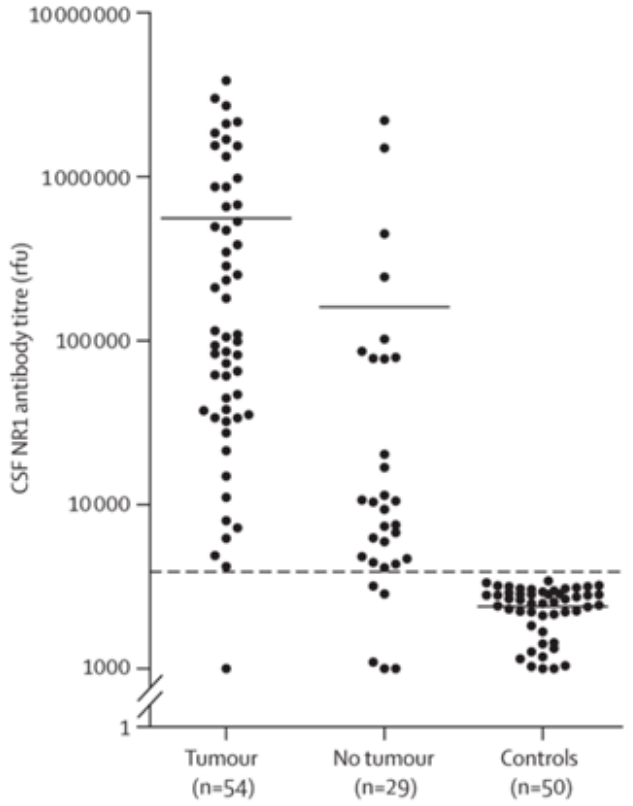
Cerebrosterol (24S-HC) Deficit Disorders

- Initial Patient Population: Smith-Lemli-Opitz Syndrome (SLOS)
  - Chronic, genetic (7-DHCR) indication
  - CNS and non-CNS deficits
  - Primarily pediatric
  - Key CNS related abnormalities:
    - Cognitive deficits, autism-like behaviors
    - Visual and auditory hypersensitivity
    - Aggression, hyperactivity, self-injury
    - Sleep disorders, opisthokinesis
  - EEG abnormalities: aberrant SWD in ~30%

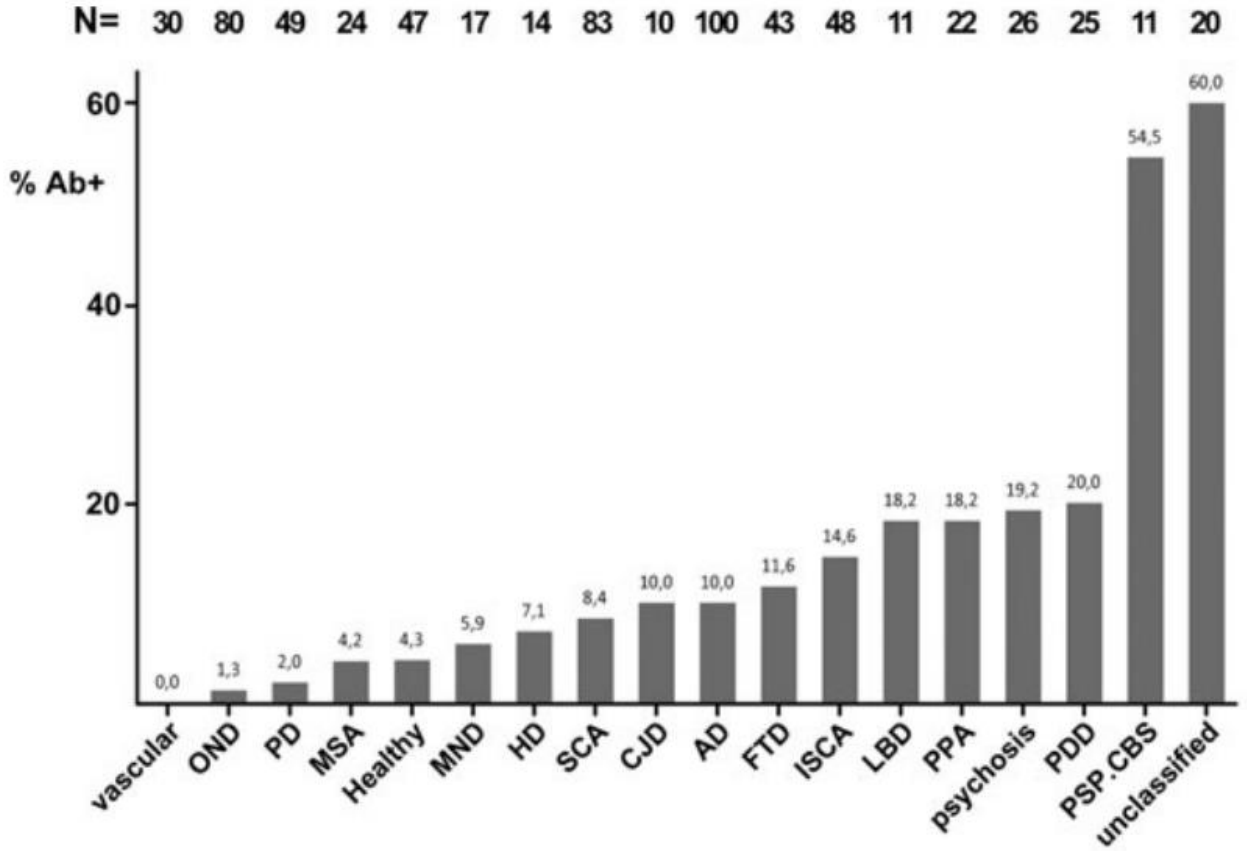
- **Expansion Indication:** Autism spectrum disorders with low 24S-HC

Role of NMDA Receptor Antibodies in Psychosis and Dementia

NMDA Antibodies are Implicated in Anti-NMDA Receptor Encephalitis[1]



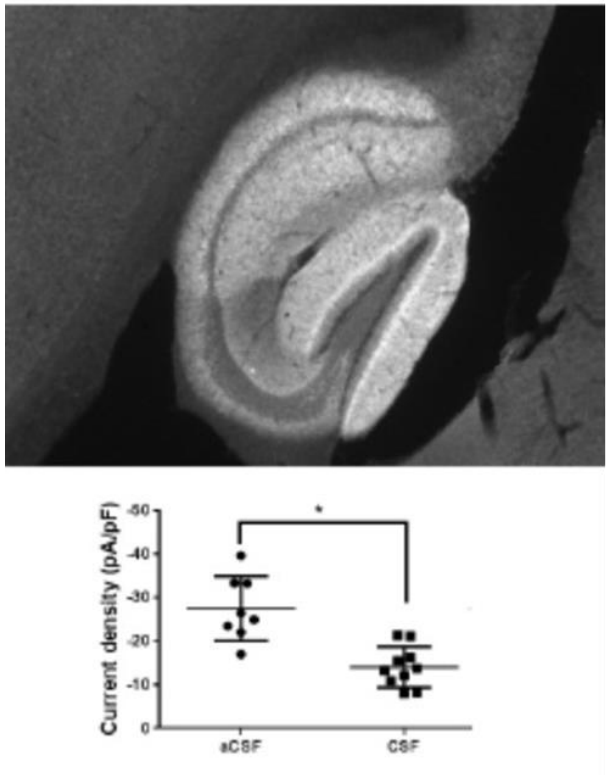
High Prevalence of IgA/IgM NMDA Antibodies in Sub-Populations of Dementia[2]

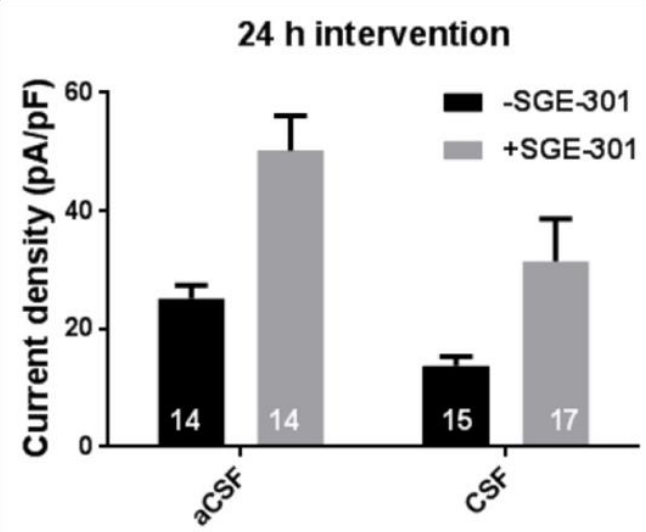


1. Dalmau et al, *Lancet Neurology*, 2008; 2. Doss et al, *Annals of Clinical and Translational Neurology*, 2014.

Anti-NMDA Treatment: Preclinical Proof-of-Concept

- Early work with ANRE patient CSF samples established that NMDA receptors are significantly downregulated (via endocytosis) and this loss of surface expression significantly decreases NMDA currents
- Deficits in NMDA function have been replicated *in vitro* using CSF from a newly identified ANRE patient; a Sage NMDA PAM can restore inhibited NMDA currents





Cerebrosterol Deficit (CSD) Disorders

A Potential Diagnostic Factor Impacting Multiple CNS Conditions

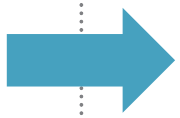
CSD Disorders

Differential diagnostic:

- Often associated with in-born errors in metabolism
- 24S-HC below age matched controls

Shared Clinical Phenotypes:

- Intellectual disabilities
- Self-injurious behaviors
- Sensory hypersensitivity
- Aggression / irritability
- Sleep fragmentation
- Attention



Potential Patient Pools

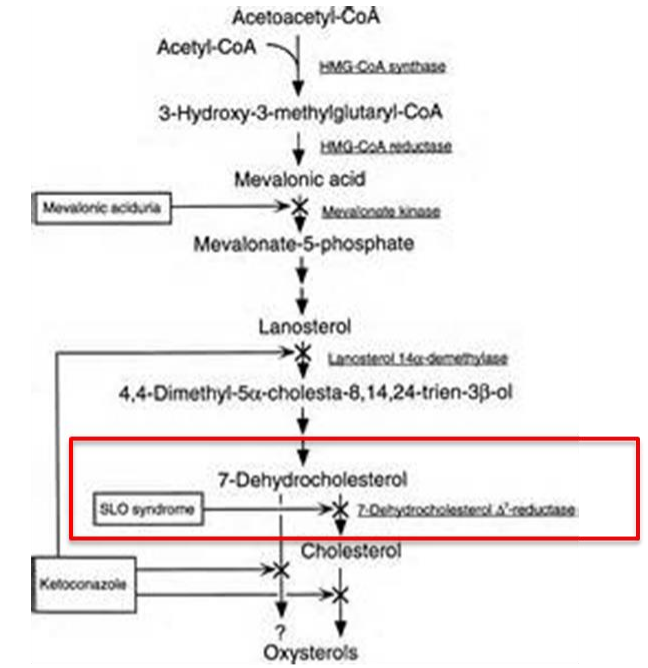
- Smith-Lemli-Opitz
- Niemann-Pick
- Autism Spectrum Disorders
- Parkinson's Psychosis
- Huntington's Disease
- PKU (cognitive impairment)
- Aggressive personality disorders
- Other disorders with in-born errors in cholesterol metabolism

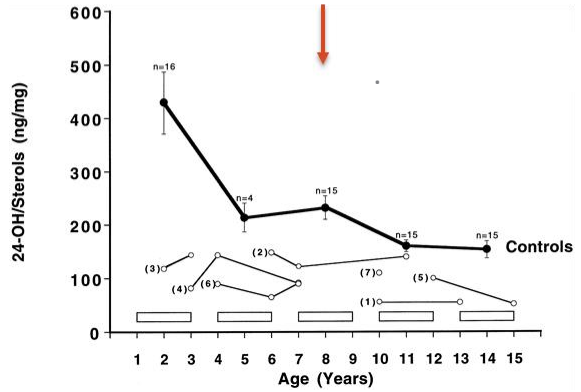
- All conditions with documented changes in 24S-HC and/or cholesterol processing

Smith-Lemli-Opitz Syndrome

Rare Genetic Disorder Associated with Impaired Cholesterol Synthesis

- SLOS is a rare autosomal recessive metabolic disorder
- SLOS is caused by mutations (>120 to date) in the DHCR7 (7-dehydrocholesterol reductase) gene
- Severity of symptoms correlate with extent of cholesterol deficiency
- Behavioral / CNS symptoms: Mental retardation, sensory hypersensitivity, aggressiveness, hyperactivity, self-injurious behaviors, opisthokinesis, sleep-disorders, and other autism spectrum behaviors
- **SLOS associated with a reduction in plasma 24S-HC[1]**





1. Björkhem et al, *J Lipid Res*. 2001.

Huntington's Disease as a Pilot Phase 1b Patient Population

Potential Link Between 24S-HC and Emotion

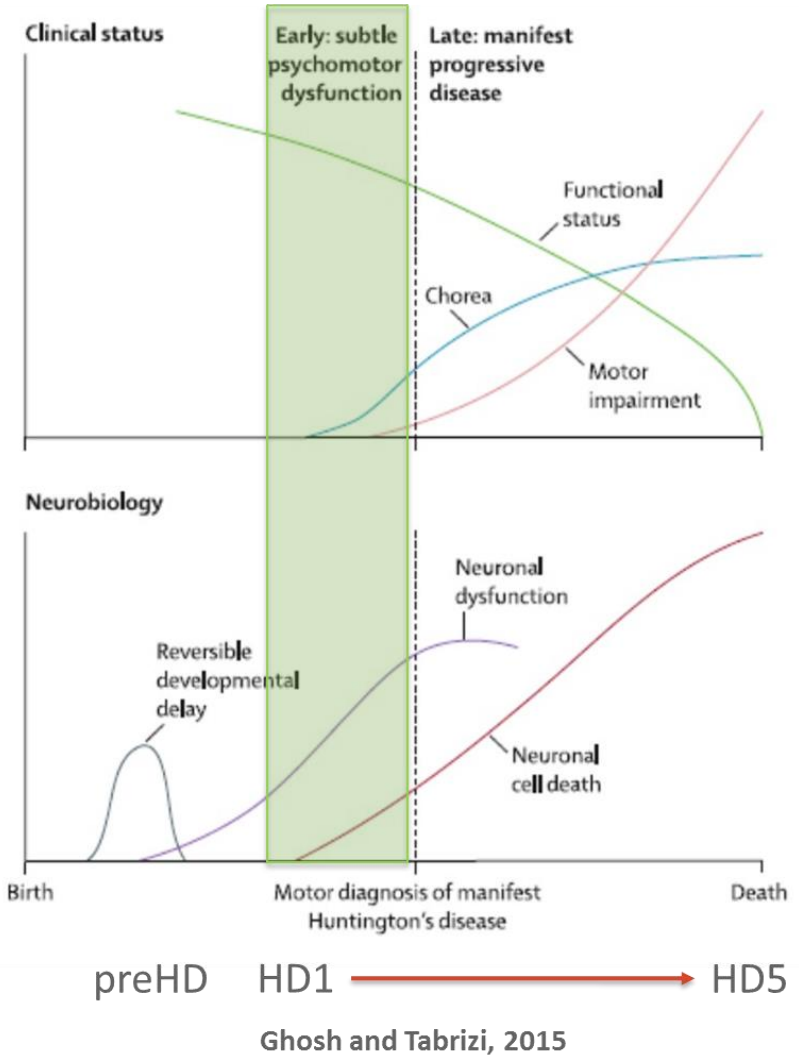
Why conduct patient biomarker study in Ph1?

- NMDA PAMs (as opposed to antagonists) are thought to enhance brain function at therapeutic doses
- Healthy volunteer studies may not be good for signal detection due to potential 'ceiling' effects

Why Huntington's Disease?

- 'Homogenous', genetically defined patient population
- Clear and consistent evidence of cognitive and neuropsychiatric effects prior to onset of severe motor symptoms (preHD to HD transition period)
- Cholesterol processing is severely disrupted in HD – with 24S-HC levels decreasing early in disease process

Access to well-phenotyped patient samples from CHDI Foundation – allows for generation of biomarker hypothesis



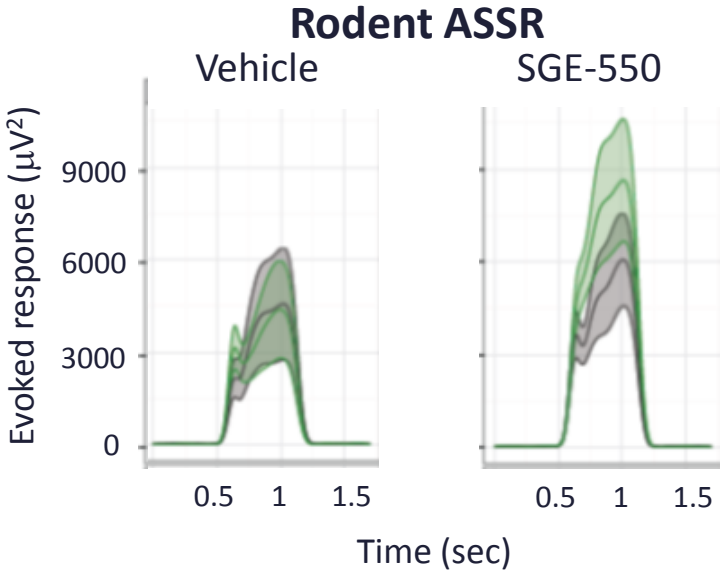
Ghosh and Tabrizi, 2015

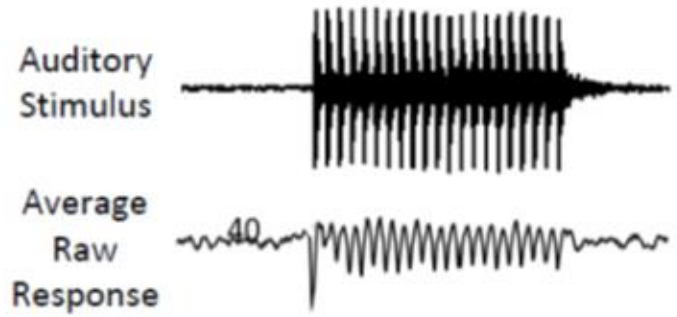
Source: Ghosh R, Tabrizi SJ, *Curr Top Behav Neurosci*, 2015.

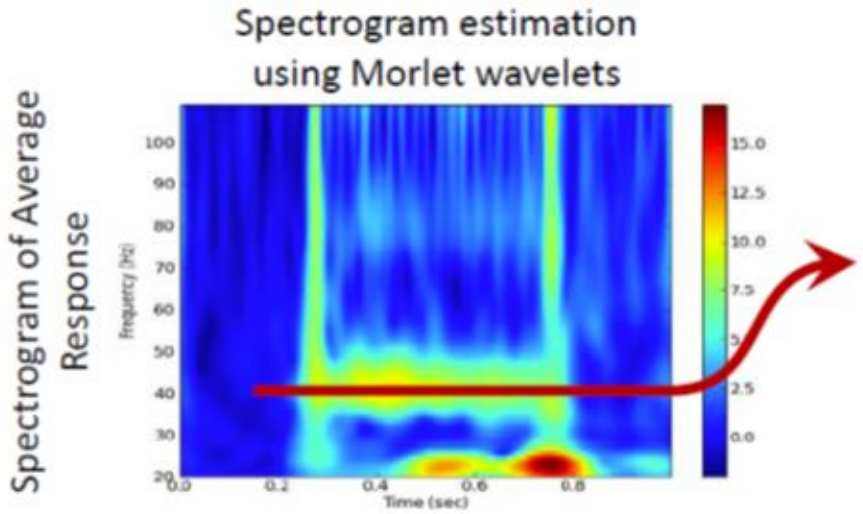
NMDA PAMs: Establishing CNS Target Engagement

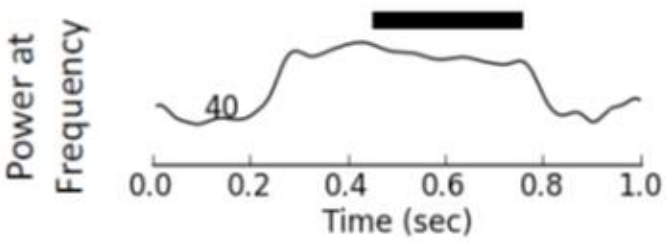
Preclinical Studies Provide Evidence that NMDA PAMs can Alter Evoked Brain Potentials

- **Auditory steady-state response (ASSR)** recorded by EEG is elicited by repetitive auditory stimulus trains
- ASSR achieves maximal spectral power in the gamma frequency range
- ASSR is reduced in schizophrenia / NMDA antagonists
- **Hypothesis:** NMDA PAMs will increase ASSR Response







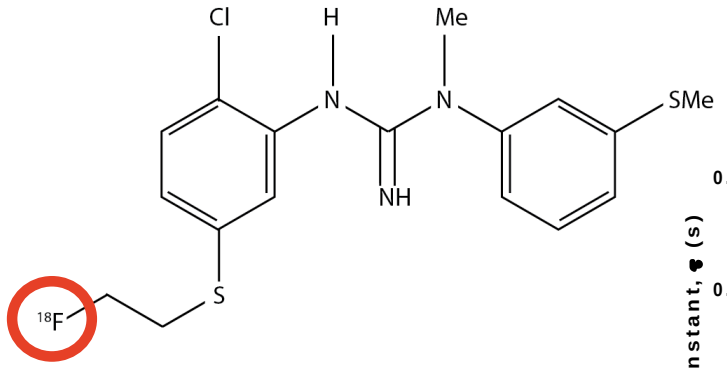


Brain Imaging: Preclinical Studies

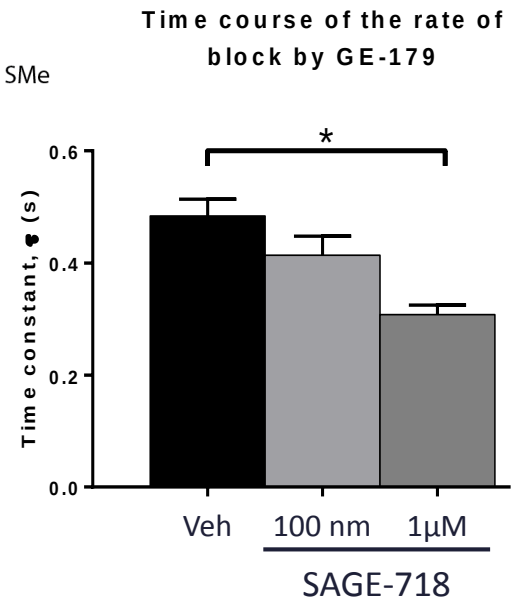
Interaction Between SAGE-718 and NMDA Channel Blocking PET-Ligand

Pilot preclinical study suggest potential for SAGE-718 to alter the binding properties of a clinically available PET ligand; however, variability deemed to high for use; other imaging technologies (i.e. fMRI, BOLD) under investigation

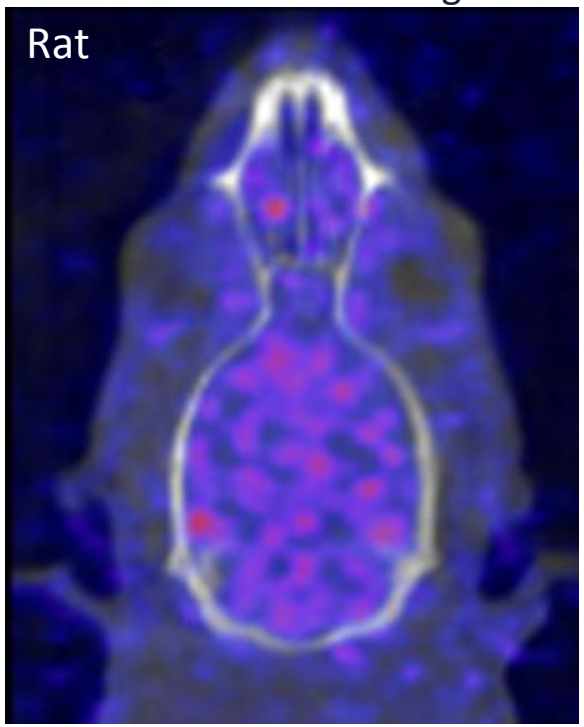
18F-GE-179: NMDA channel PET Ligand



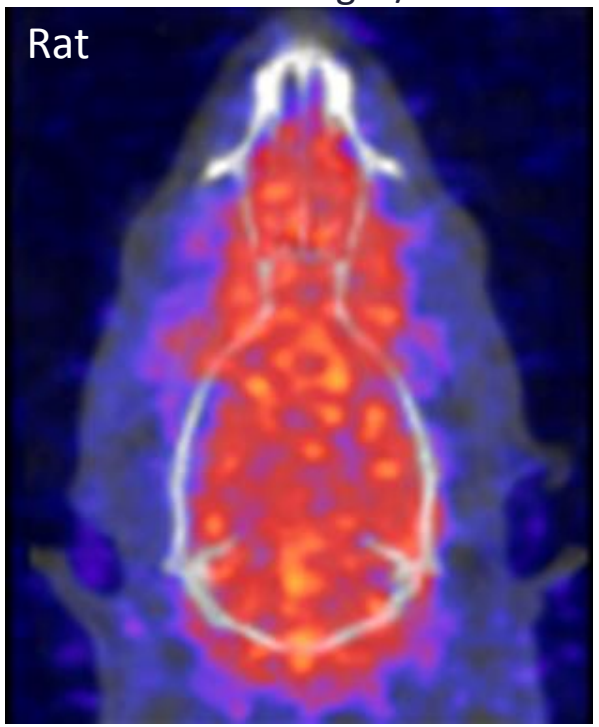
SAGE-718 alters kinetics of GE-179



18F-GE-179 binding



18F-GE-179 binding w/ SAGE-718

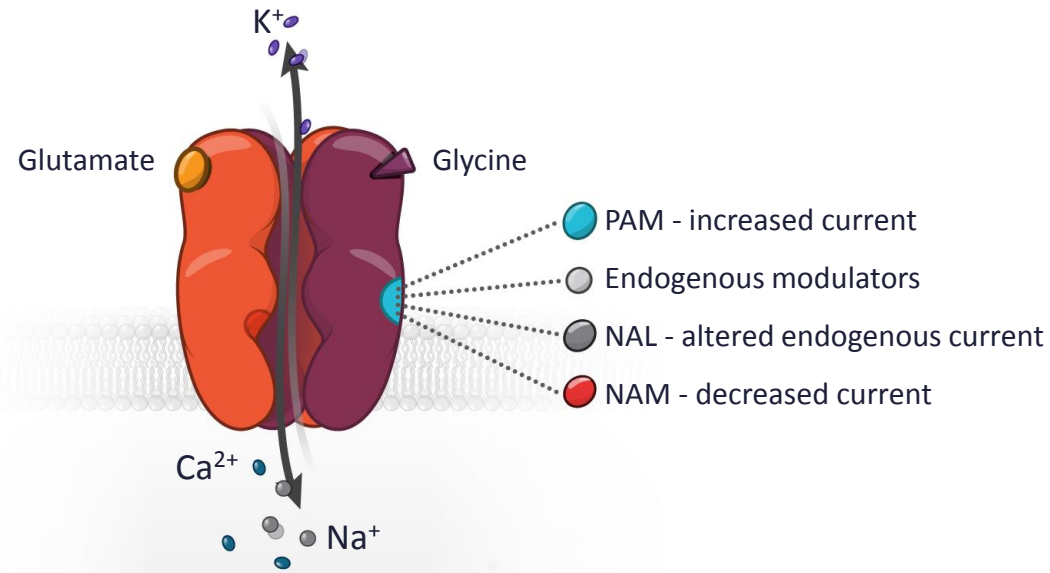


Next Generation Programs Build on Rich Sage Science

Exploratory		Target Validation / Hit ID		Hit to Lead
NMDA-2C/D PAM	↑NAS biosynthesis	GABA Hypofunction	NMDA Neutral ligand	NMDA NAM
GABA NAM	↑ Oxysterol biosynthesis	GABA+	Tourette's	Extrasynaptic $GABA_A$ PAM

Oxytesterol Biology

inflammation	Neuroinflammation	Autoimmune disease
neuroprotection	Neuroprotection	
metabolism		Metabolism



Sage is Pursuing Innovative R&D through Translation

- Pursue validated and novel translational approaches to improve probability of success
  - Identify functional and biochemical biomarkers and deploy for translation
  - Focus on establishing target engagement and dose selection early
- Employ preclinical validation and human proof-of-concept for read-through
- Establish translational foundation across discovery and clinical programs

SAGE THERAPEUTICS™

Q&A

SAGE THERAPEUTICS™

Developing SAGE-547

Steve Kanes, MD, PhD - CMO

Sage's Differentiated Approach to Development

Strategies to Accelerate Development of Potential Medicines through Multi-Dimensional Approach

Intentional

- Advancing novel therapies through our understanding of the disease biology and translational findings

Efficient

- Pursue rapid timelines through strategies that reflect sound regulatory approaches and good development science

Systematic

- Leading with early human proof-of-concept before indication expansion based on scientific rationale and clinical data findings
- Focusing on clear trial design to produce unequivocal clinical data to allow informed go/no-go decisions

Incremental Innovation

Advancing Novel Medicines through Deliberate and Data-Driven Development

Scientific Rationale

- Disease biology
- Role of mechanism
- Translatable animal models
- Right patient population

Early Proof-of-Concept

- Open-label signal finding
- Proof of activity
- Increased investment for next development phase
- Methodology for future studies

Controlled Validation

- Definitive, late-stage
- Multi-center, global
- Replicate earlier studies
- Goal to generate valuable data for regulatory discussions

SAGE-547 Dual Development Path

	Completed		Ongoing Efficacy Studies
SRSE	**Emergency Use** 11 patients	**Phase 1/2** Open-Label 25 patients	STATUS TRIAL **Phase 3** Placebo-controlled ~140 patients
PPD	**Phase 2a** Open-label 4 patients	**Phase 2** Placebo-controlled 21 patients	HUMMINGBIRD **Phase 3** Placebo-controlled ~220 total patients

Two patient populations significantly underserved by current treatments

Abbreviation: SRSE, super-refractory status epilepticus; PPD, postpartum depression.

SAGE-547 as a Treatment for PPD

Intended as an interventional acute therapy

Phase 3 HUMMINGBIRD Study

- Severe PPD study: Placebo-controlled, multi-center, dose-ranging
- Moderate PPD study: Placebo-controlled, multi-center

Study 301

- Open-label, multi-center safety study

NEST PROGRAM

HUMMINGBIRD

If approved, SAGE-547 would be first treatment specifically for PPD

SAGE THERAPEUTICS

PPD SAGE-547 Regulatory Status

- FDA Breakthrough Therapy Designation
- Current Phase 3 PPD program, if successful, considered suitable for NDA filing
- Eligible for Priority Review

- EMA PRIME designation
- Eligible for accelerated assessment for MAA filing
- Plan to seek EMA Scientific Advice

Regulatory designations provide potential accelerated pathways in U.S. and EU

Abbreviation: SRSE, super-refractory status epilepticus; PPD, postpartum depression.

SAGE-547 PPD Development Update

	Pre-BTD/PRIME	Now
Development Stage	• Phase 2 • U.S.	• Phase 3 • U.S., Canada, Europe
Ongoing Efficacy Studies	• 202B – Severe (~60 patients) • 202C – Moderate (~36 patients)	• 202B – Severe (~120 patients) • 202C – Moderate (~100 patients)
Safety Study		• Study 301 – open-label safety study
Primary Endpoint	• HAM-D total score • SAGE-547 vs placebo at 60 hours	• Unchanged
Follow-up	• Day 30 follow-up	• Unchanged

SAGE-547 as a Treatment for SRSE

Intended as an interventional adjunctive therapy in an acute critical care setting

Phase 3 STATUS Trial

- Placebo-controlled, multi-center

Study 302 Expanded Access Protocol

- Open-label, multi-center
- Designed to make SAGE-547 available to SRSE patients in U.S. at non-STATUS Trial clinical sites

No approved therapies for the treatment of SRSE

SRSE SAGE-547 Regulatory Status

- Orphan Drug Designation
- FDA Fast Track Designation
- Phase 3 Special Protocol Assessment
- Eligible for Priority Review

- Positive EMA Scientific Advice
- Plan to seek MAA based on current Phase 3 SRSE program, if successful

Agreement with U.S. and EU regulators on registration path

Abbreviation: SRSE, super-refractory status epilepticus; PPD, postpartum depression.

SAGE-547

Two Near-Term Opportunities

	SRSE	PPD
Regulatory Designations:	• Fast Track (U.S.) • Orphan Drug (U.S.)	• Breakthrough Therapy (U.S.) • PRIME Designation (EU)
Estimated U.S. Patient Population:	• ~25,000 – 41,000 in per year[1]	• ~500,000 - 750,000 pear year[2,3] • Up to 80% moderate-severe[4]
Expected Treatment Setting:	• ICU, Neuro-ICU	• Hospital, holding unit, psych facility or home infusion
Preliminary Pricing Assumptions:	• $25,000 - $75,000 per patient	• Proportional patient pricing

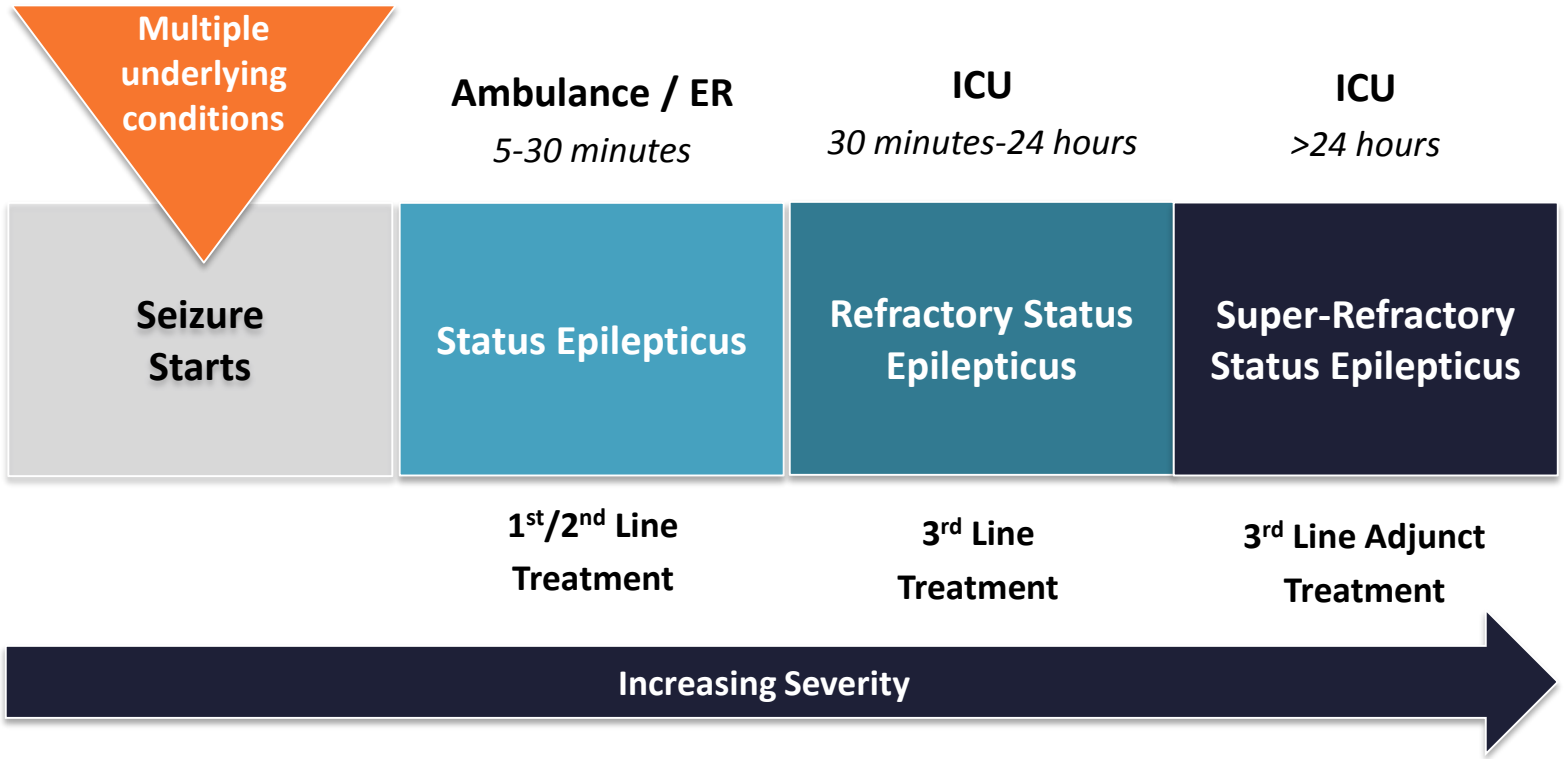
1. Beg et al. *Journal of Medical Economics,* 2016. 2. Hamilton et al. *National Vital Statistics Reports*. National Center for Health Statistics, 2015. 3. O'Hara MW & McCabe JE. *The Annual Review of Clinical Psychology,* 2013. 4. PACT. Lancet Psychiatry. 2015.

SAGE-547 in SRSE

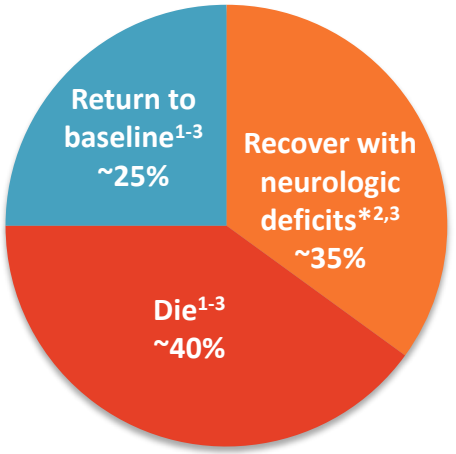
Eric Rosenthal, MD - MGH

Progression of SE into SRSE

Super-refractory status epilepticus (SRSE) is a life-threatening neurologic emergency that occurs after ≥24 h in status epilepticus (SE), despite multiple therapeutic interventions (first-, second-, and third-line agents)



Estimated SRSE outcome rates[1,2,3]



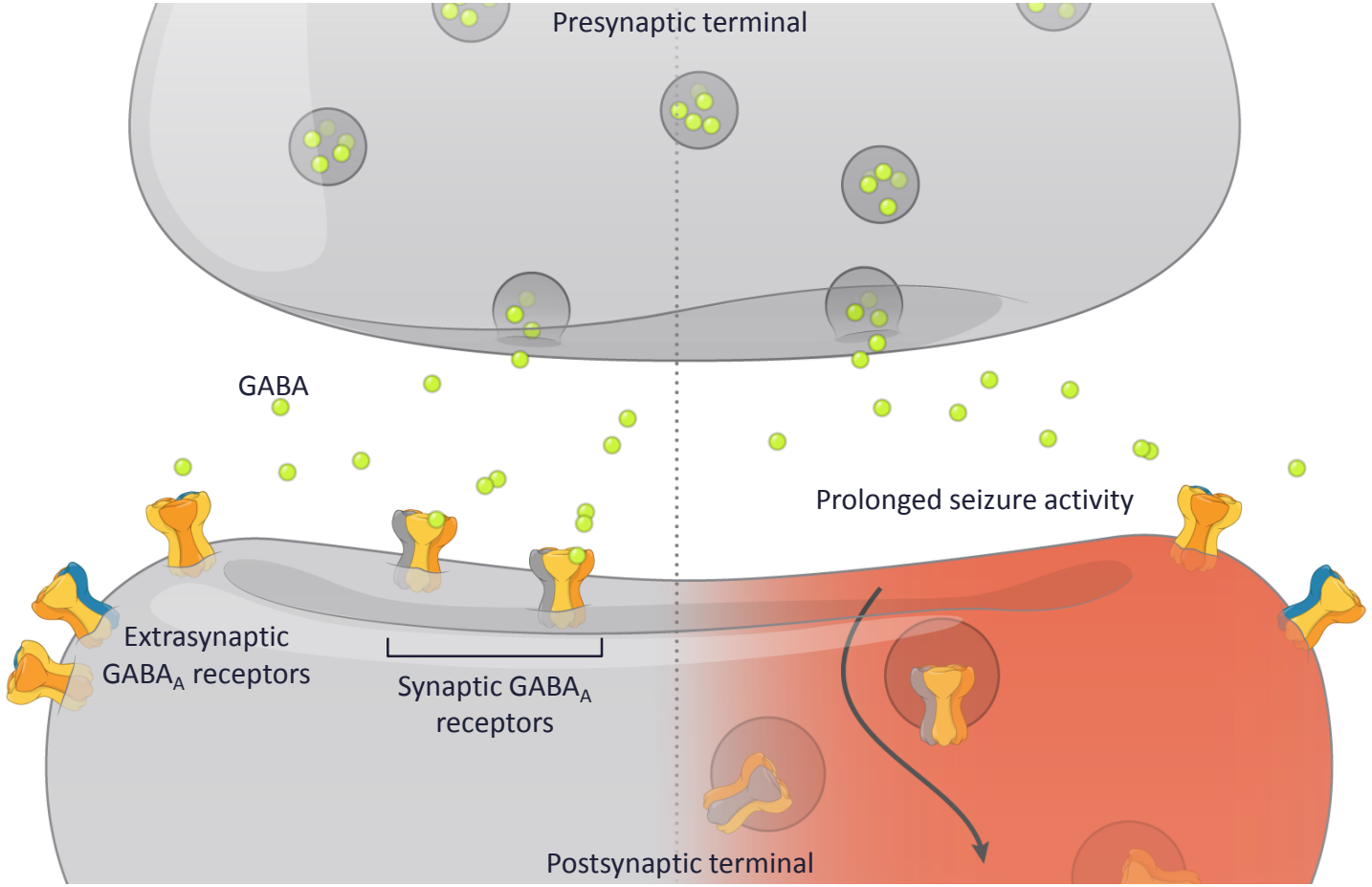
* ~ 15% severe,
* ~ 15% mild,
* ~ 5% undefined[2]

>60% of patients with SRSE die or remain severely disabled[2]

1. Shorvon et al. *Brain*. 2012;135(8):2314-28. 2. Novy et al. *Epilepsia*. 2010;51(2):251-6. 3. Claassen et al. *Epilepsia* 2002; 43(2): 146-153.

SRSE Pathophysiology

Inhibitory $GABA_A$ Receptors May Play an Important Role in SRSE



Reduction in inhibitory $GABA_A$ receptors

- During SRSE, increased receptor trafficking leads to an overall reduction in functional $GABA_A$ receptors

Changes in conformation of $GABA_A$ receptors

- SRSE induces functional changes in the hippocampal $GABA_A$ receptors, leading to $GABA_A$ isoforms with different pharmacological characteristics

Changes in extracellular ionic environment

- GABA-mediated currents that are normally inhibitory may become excitatory following changes in extracellular chloride concentrations

SRSE Etiology is Diverse

Potential Causes of SRSE

Structural Causes

- Cerebrovascular
- Metabolic
- Tumors
- Medication induced/overdose
- Immunological disorders
- Mitochondrial disorders

Non-structural Causes

- Hypoxic
- Low antiepileptic drug levels
- Alcohol
- Trauma
- CNS infections
- Infectious diseases
- Drugs/toxins
- Genetic disorders

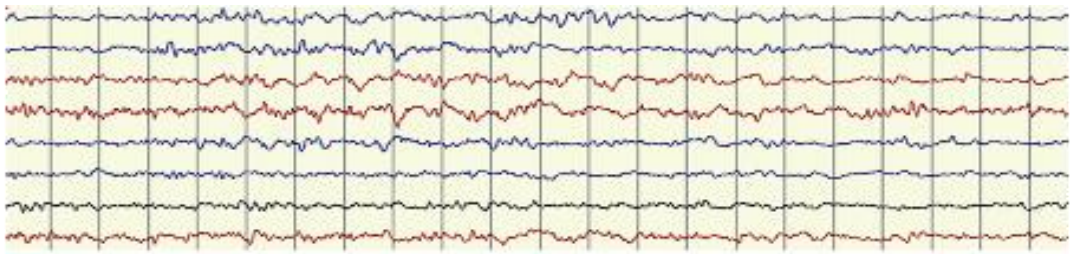
Unknown Causes

- For 19-30% of SE cases there is no identifiable cause

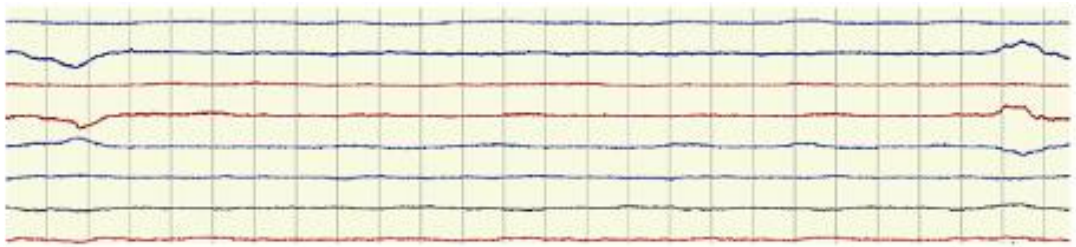
Sources: Kinney M, Craig J, *Ulster Med J.* 2015; Trinka E, Höfler J, Zerbs, *Epilepsia*, 2012; Neligan A, Shorvon SD, *Arch Neurol*, 2010.

Diagnosis and Continuous EEG (cEEG)

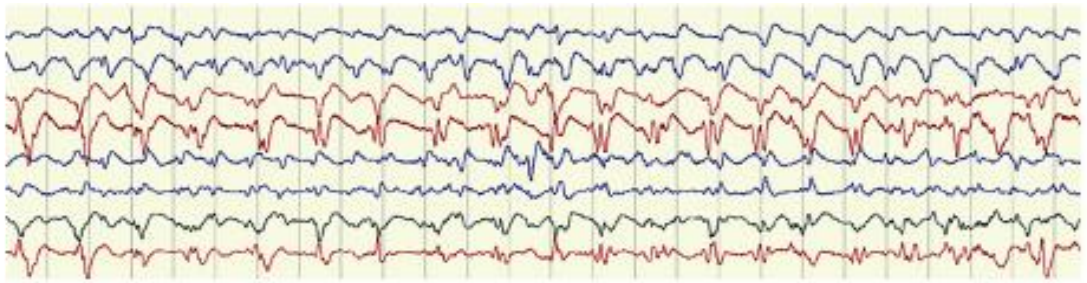
- Diagnosis made by clinical assessment and supported by continuous EEG monitoring
- cEEG monitoring is vital for monitoring mental status in SRSE patients
- SE is often non-convulsive (NCSE)
- cEEG can detect NCSE or early ischemia, which would not be detected and diagnosed by occasional 20-minute-long routine EEGs, careful clinical neurologic examination, or neuroimaging tests



normal



suppression



seizure

Treatment of SRSE

- Primary goal in SRSE treatment is to suppress seizure activity as soon as possible in order to minimize excitotoxic cerebral damage, while minimizing long term exposure to IV general anesthetics and other third-line agents
- SRSE is commonly managed in ICU by inducing either sustained seizure suppression or deeper near-complete EEG suppression ("burst suppression") using continuous IV general anesthetics
- Goal of burst suppression is to allow the brain and corresponding neuronal tissue to restore function and reset to normal pre-seizure levels
- Treatment of SRSE is considered successful when a patient breaks status and does not revert back within 24 hours

Potential Serious Side Effects with Current Standard of Care

	Midazolam	Propofol	Pentobarbital	Ketamine
Mechanism of Action	GABA activity	GABA activity; NMDA antagonist properties	GABA activity; barbiturate	NMDA antagonist
Half-Life (Hours)	2-7*	0.5-7*	15-50*	2.5
Metabolism	Hepatic	Hepatic	Hepatic	Hepatic
Drug Interactions	CYP 3A4 substrate	N/A	CYP 2A6 inducer	CYP 2C9 & 3A4 substrate
Adverse Reactions	• Hypotension • Respiratory depression	• Hypotension • Respiratory depression • Propofol-related infusion syndrome (PRIS) • Triglyceride increase	• Hypotension • Respiratory depression • Paralytic ileus • Immune suppression • Hepatic / pancreatic dysfunction • Body temperature increase • Propylene glycol toxicity	• Hypertension • Hyper-salivation • Hallucinations • Emergence reaction: as such typically requires co-administered anesthetics

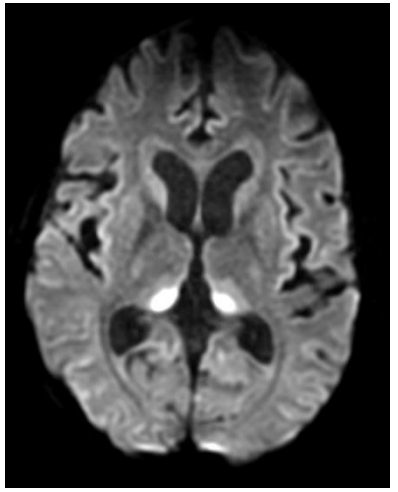
*Duration may be prolonged with extended duration of use.

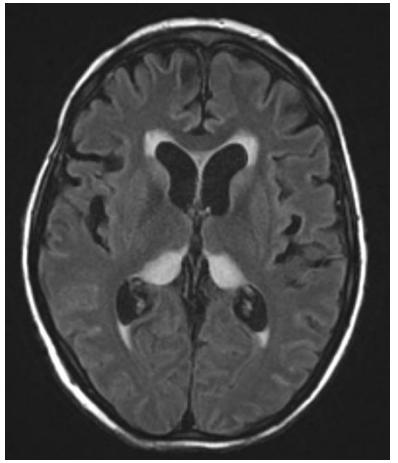
Source: Reznik et al, *Journal of Clinical Medicine*, 2016.

SRSE Case Presentation #1

Neurologic Complications of Seizure

- **History:** 28 yo woman developed a viral syndrome and then new-onset status epilepticus. She had a history of newborn seizures on day 2 and day 4 of life.
- **Neuroimaging:** MRI initially negative. Lumbar puncture showed WBC 7 (92% N), TP 68, Glu 63 in CSF
- **EEG:** slow with right greater than left lateralized periodic discharges.
- **Infectious:** CSF/serum: WBC 7 (92% N), TP 68, Glu 63 in CSF. Negative for bacterial Cx, West Nile, Enterovirus, HSV, Eastern Equine, HIV, CMV, EBV, VZV, HHV-6, lyme, rabies, bartonella
- **Brain biopsy:** Negative for HSV, Adenovirus, EBV, CMV, Viral Cx, Bacterial Cx, Fungus, AFB
- **Autoimmune/Paraneoplastic testing:** Negative for C3/C4 complement, ANCA, RPR, RF, ANA, ESR, CRP, SPEP; Anti- Sm, DS DNA, thyroglobulin, NMDA, VGKC, CV2, Hu, Ma, Ta, Amphiphysin, ANNA-1, ANNA-2, ANNA-3, AGNA-1, PCA-1, PCA-2, PCA-Tr, CRMP-5. Transvaginal US x 3 w/o evidence of teratoma and Chest/Abd/Pelvis CT x 3 (with 1 PET-CT)
- **Toxicology:** Full tox screen negative including salicylate, EtOH, acetaminophen, etc.
- **Course:** 166-day hospital course, including treatment for encephalitis (antivirals), neuroinflammatory condition (IVIg), seizure therapies. Transferred to MGH for unconventional treatments including cooling. Developed neurologic injury from seizures (bilateral thalamic injury) and succumbed to multiple medical complications.

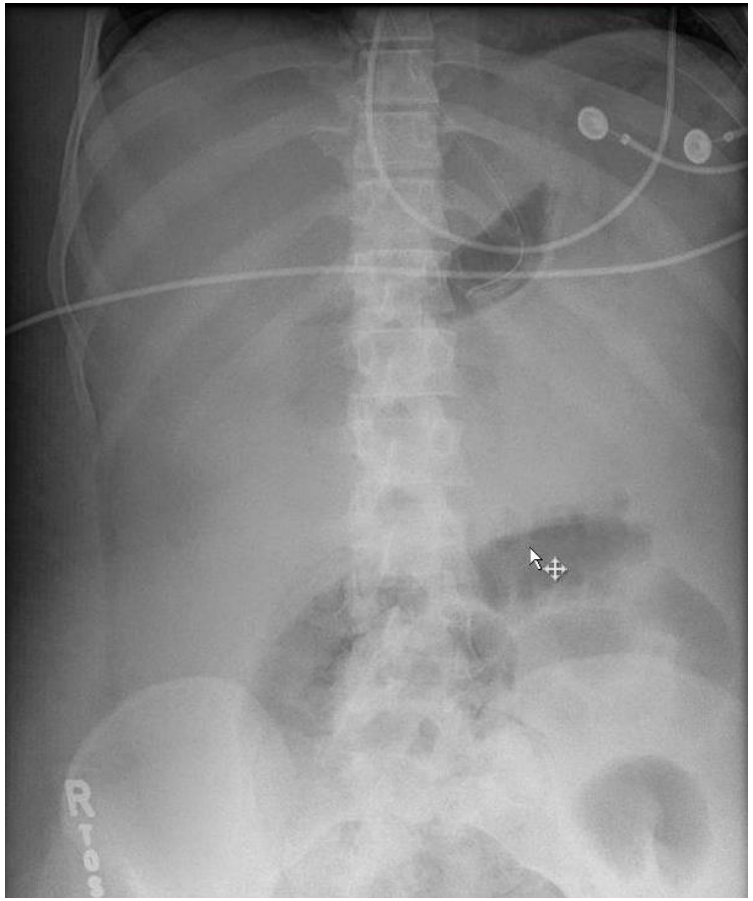




SRSE Case Presentation #2

Systemic Complications of Seizure

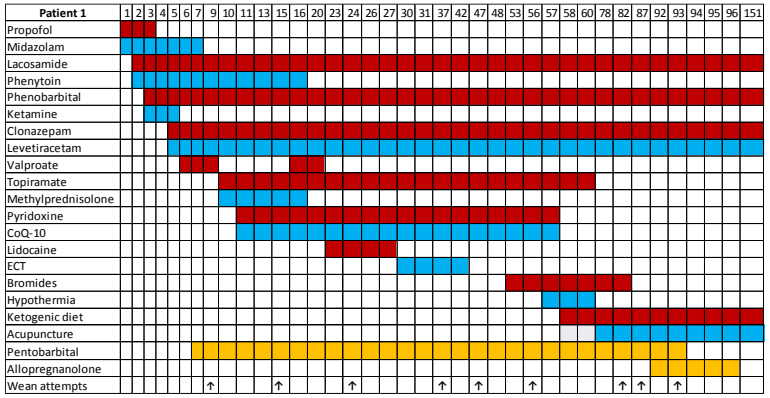
- **History:** 21-year-old man with 5-day viral symptoms followed by seizures.
- **Neuroimaging:** 3 MRIs unrevealing.
- **EEG:** Bilateral independent discharges and runs; repeated seizures upon weaning anesthetic burst-suppression.
- **Infectious:** 2 lumbar punctures without signs of meningitis
- **Course**: Treatments included hypothermia, ketamine, midazolam, ketogenic diet, phenobarbital, phenytoin, depakote, lacosamide. The patient, however, developed a large bowel ileus likely due to pentobarbital and renal failure due to hypotension. On the day of transfer to MGH he developed profound acidosis and liver failure, likely due to progression of the ileus and subsequent bowel ischemia. A colectomy was considered but the patient was felt not to be stable enough to tolerate. He died the morning after arriving.



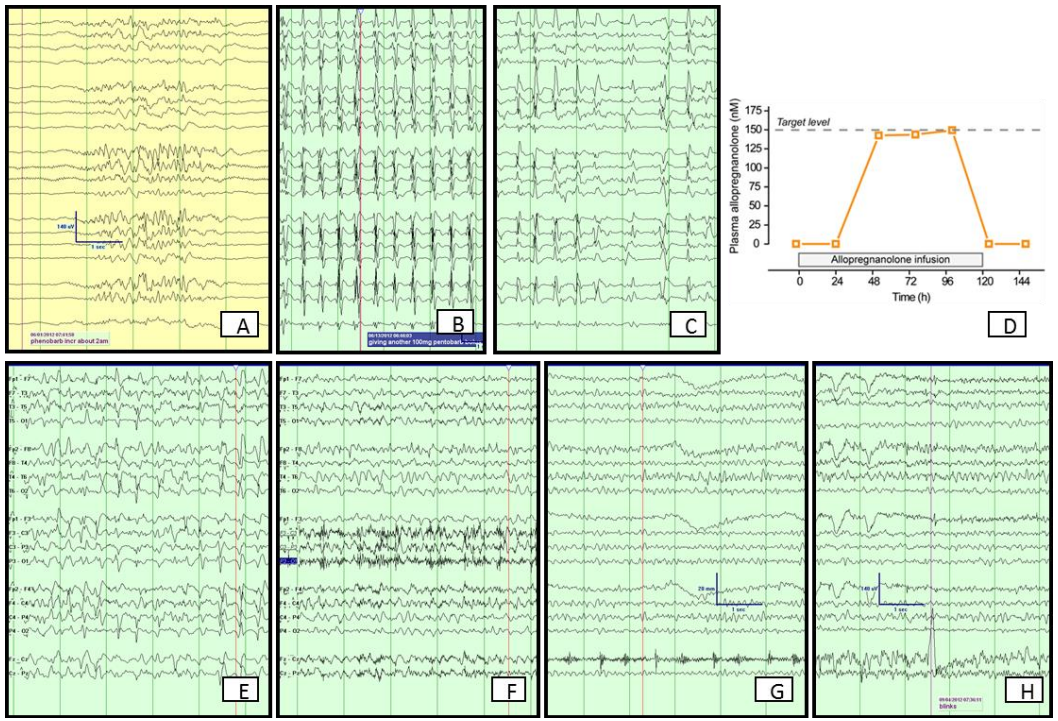
SRSE Case Presentation #3

Example of Successful Treatment

- **History:** 23 year-old man with 1 week of malaise and headache then frequent generalized seizures with myoclonic features, failing multiple therapies.
- **Diagnostics:** No clear cause for SRSE was identified.
- **Course:** Eight attempts to wean pentobarbital and multiple immunologic and AED interventions were unsuccessful. FDA approved an emergency IND for SAGE-547 Infusion as a bridge therapy to wean the patient off pentobarbital. During this 5-day infusion the patient was successfully weaned from pentobarbital.

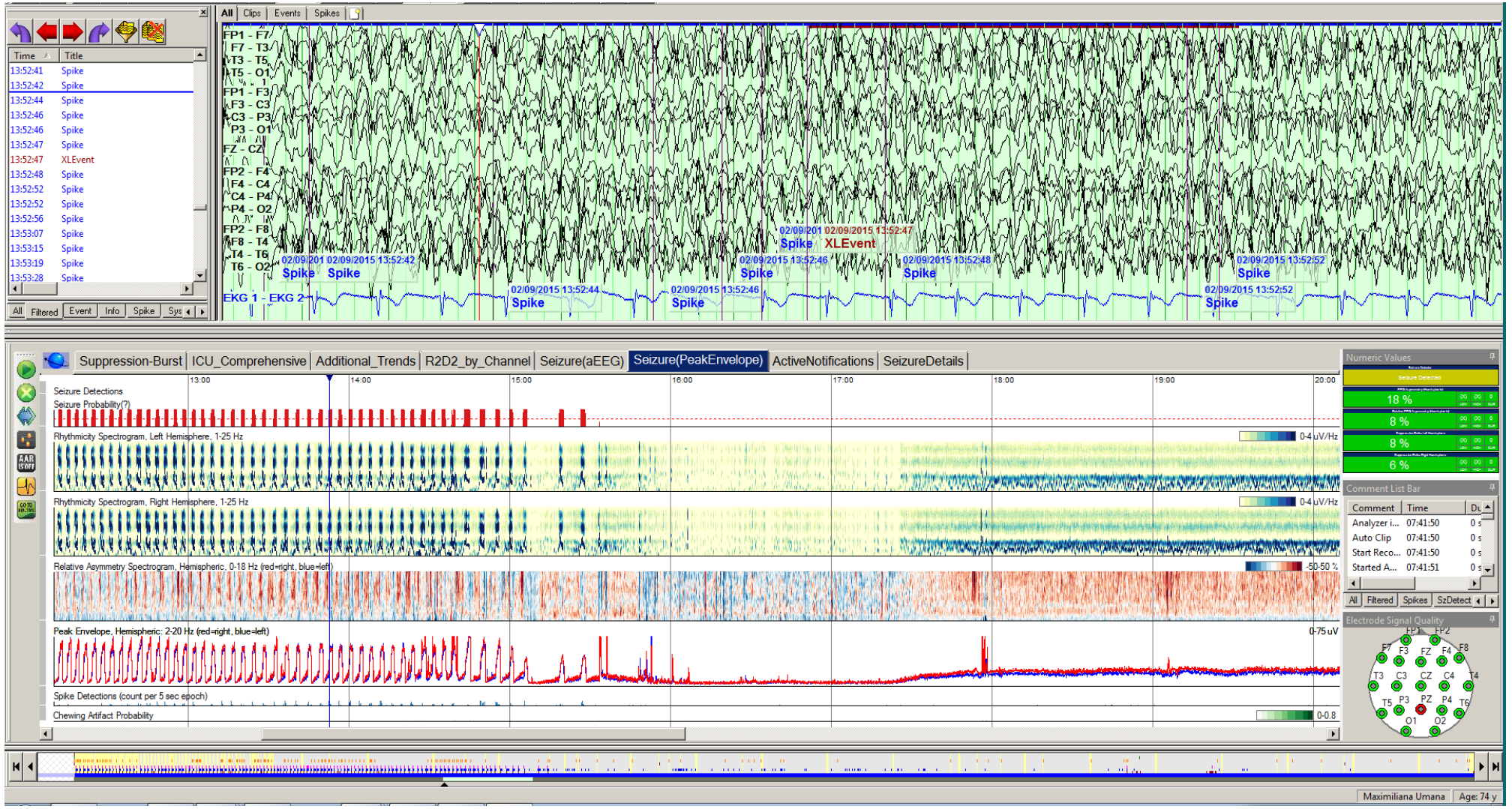


- **Follow up:** The patient continues to be cognitively intact and seizure free at 3-year follow up.



A) Burst suppression pattern, 1.5 mg/kg/h PTB. **B)** EEG PTB d.30. **C)** EEG PTB d.80 (6 mg/kg/h). **D)** arterial plasma allopregnanolone: -2h, +24h, +52h, +76h, +100h, +124h and +148 h. **E-H)** EEG normalization at 12h, 24h, 36h and 48h after PTB discontinuation while on study drug.

Example of Seizure Suppression and Trending

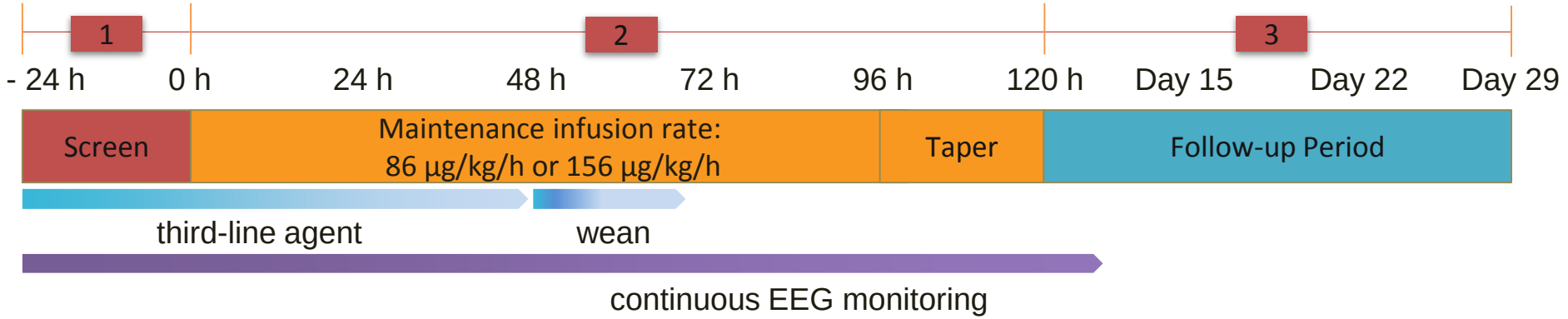


SRSE Phase 1/2 Trial Design

Trial Design: Open-label, adjunctive to SOC, age ≥2 years at 18 U.S. sites

Inclusion criteria: SE, failing 1st, 2nd, 3rd-line anesthetic (TLA) with ≥1 failed TLA wean attempt

Exclusion criteria: SRSE due to Anoxic/Hypoxic Encephalopathy



Primary endpoint: Safety, tolerability and pharmacokinetics

Secondary endpoints:

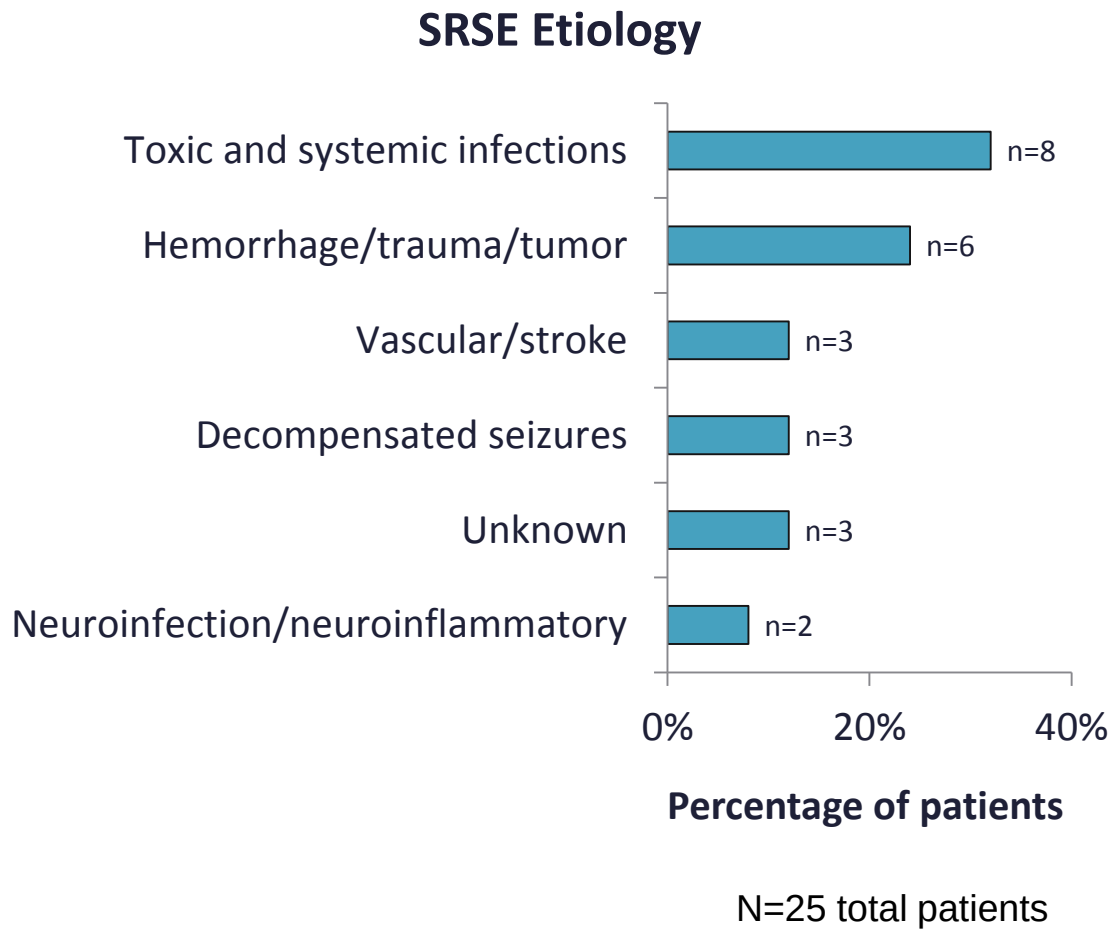
- Efficacy – wean of TLA prior to end of SAGE-547 maintenance (Response Endpoint I)
- Efficacy – wean of TLA prior to end of SAGE-547 taper (Response Endpoint II)
- GCS, CGI-S, CGI-I, modified Rankin Scale scores, survival

SRSE Phase 1/2 Patient Characteristics

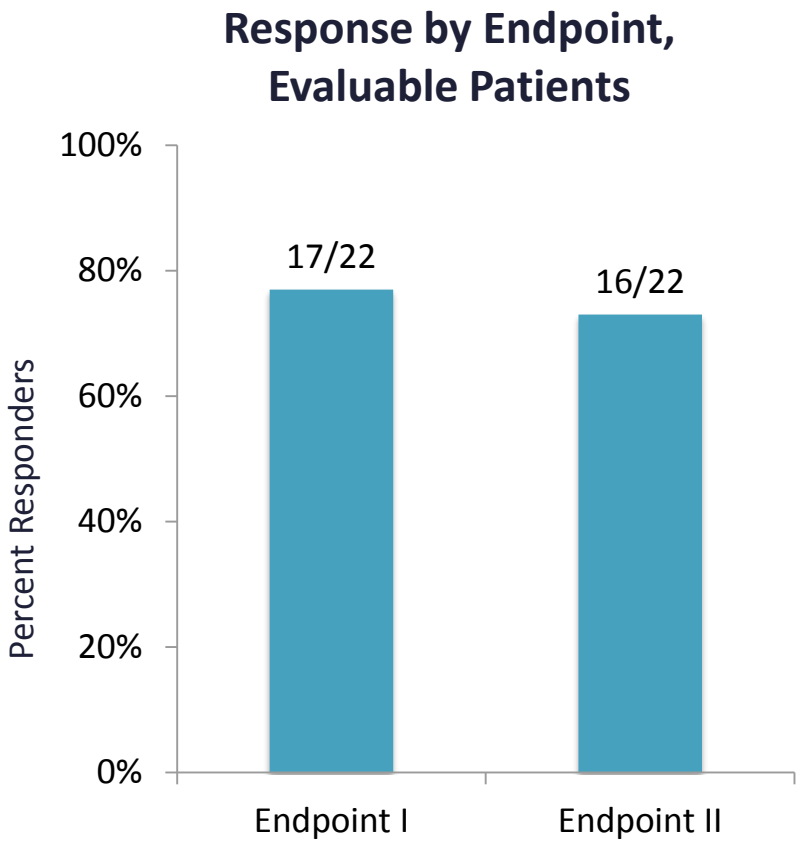
Patient Demographics	
Male	N=16
Female	N=9
Age (years)	Mean 48 (range: 10-76)
Intubated	100%

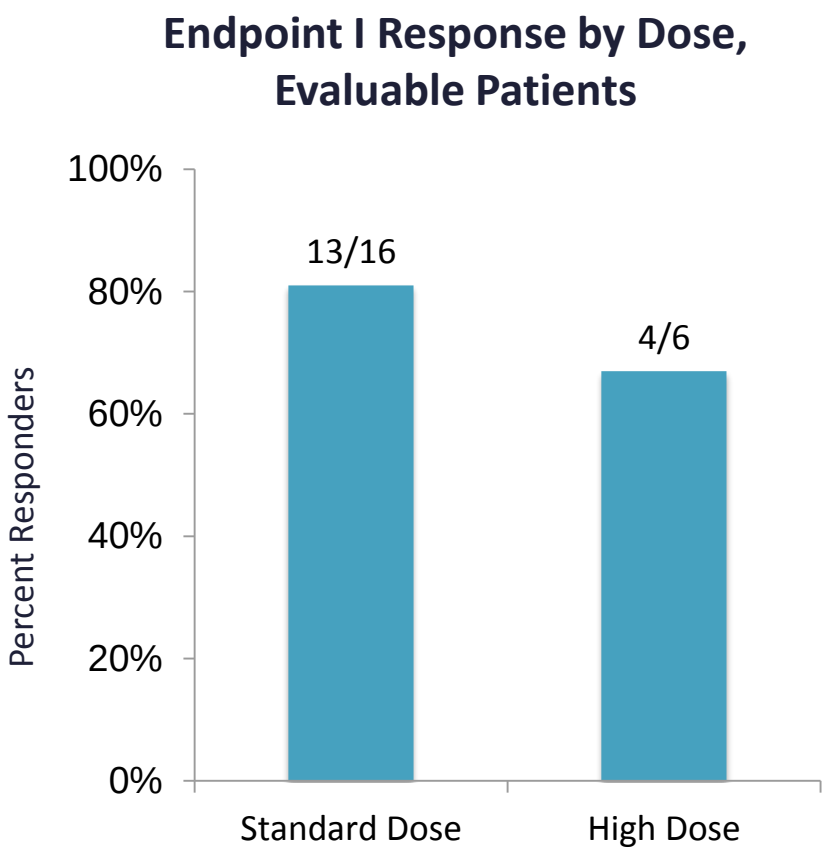
Baseline Characteristics	Mean (range)
Duration of SE (days)	9 (3-20)
Baseline STESS	3.4 (1-5)
Prior weans (n)	2.0 (0-8)
Antiepileptics (n)	3.0 (1-5)
Third-line agents (n)	1.4 (1-2)
Concurrent meds (n)	12.9 (2-24)

*STESS: Status Epilepticus Severity Score



SRSE Phase 1/2 Trial Results





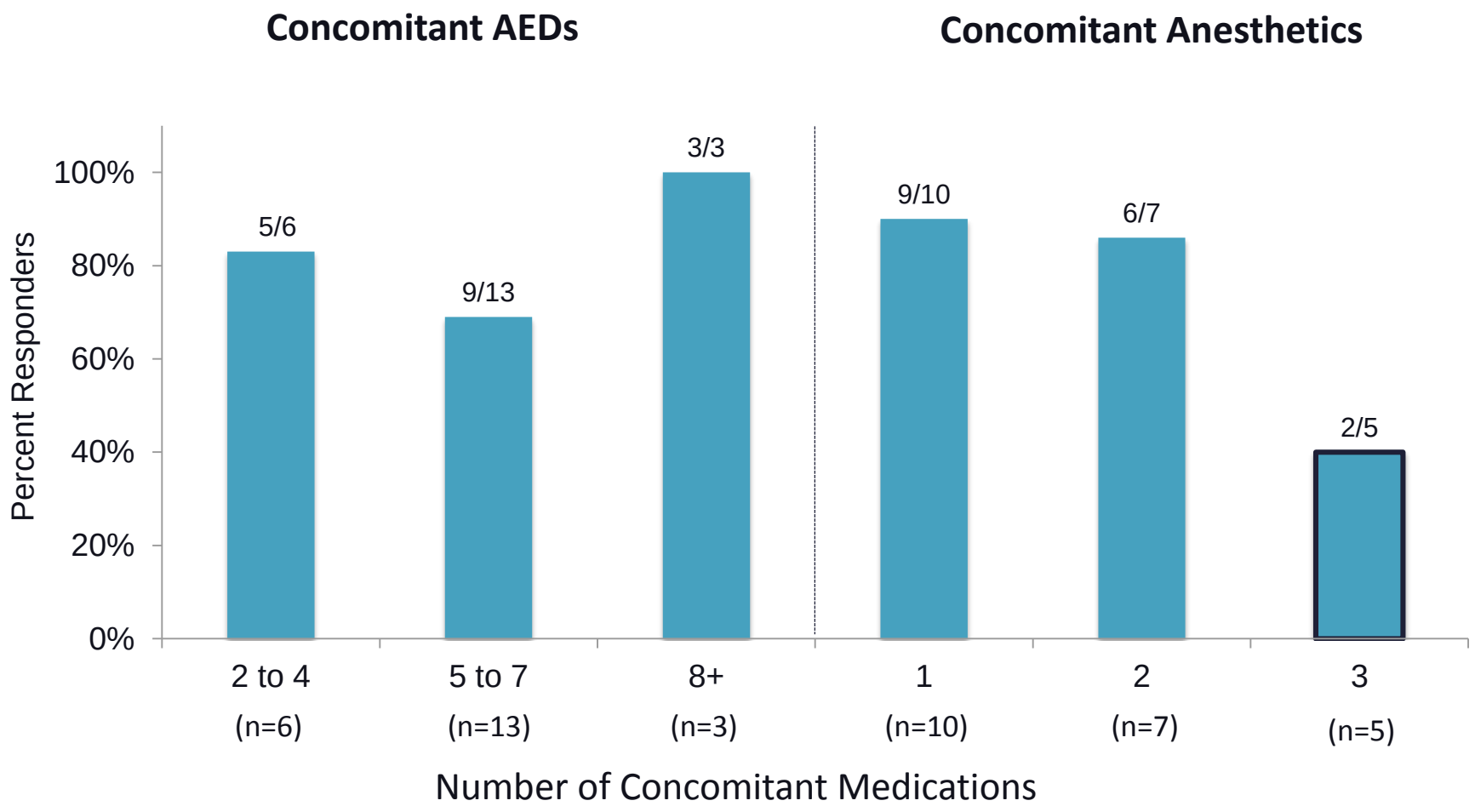
Endpoint I: wean of TLA prior to end of SAGE-547 maintenance

Endpoint II: wean of TLA prior to end of SAGE-547 taper

N=22 total evaluable patients

SRSE Phase 1/2 Trial Results

Response in Relation to Patient Characteristics

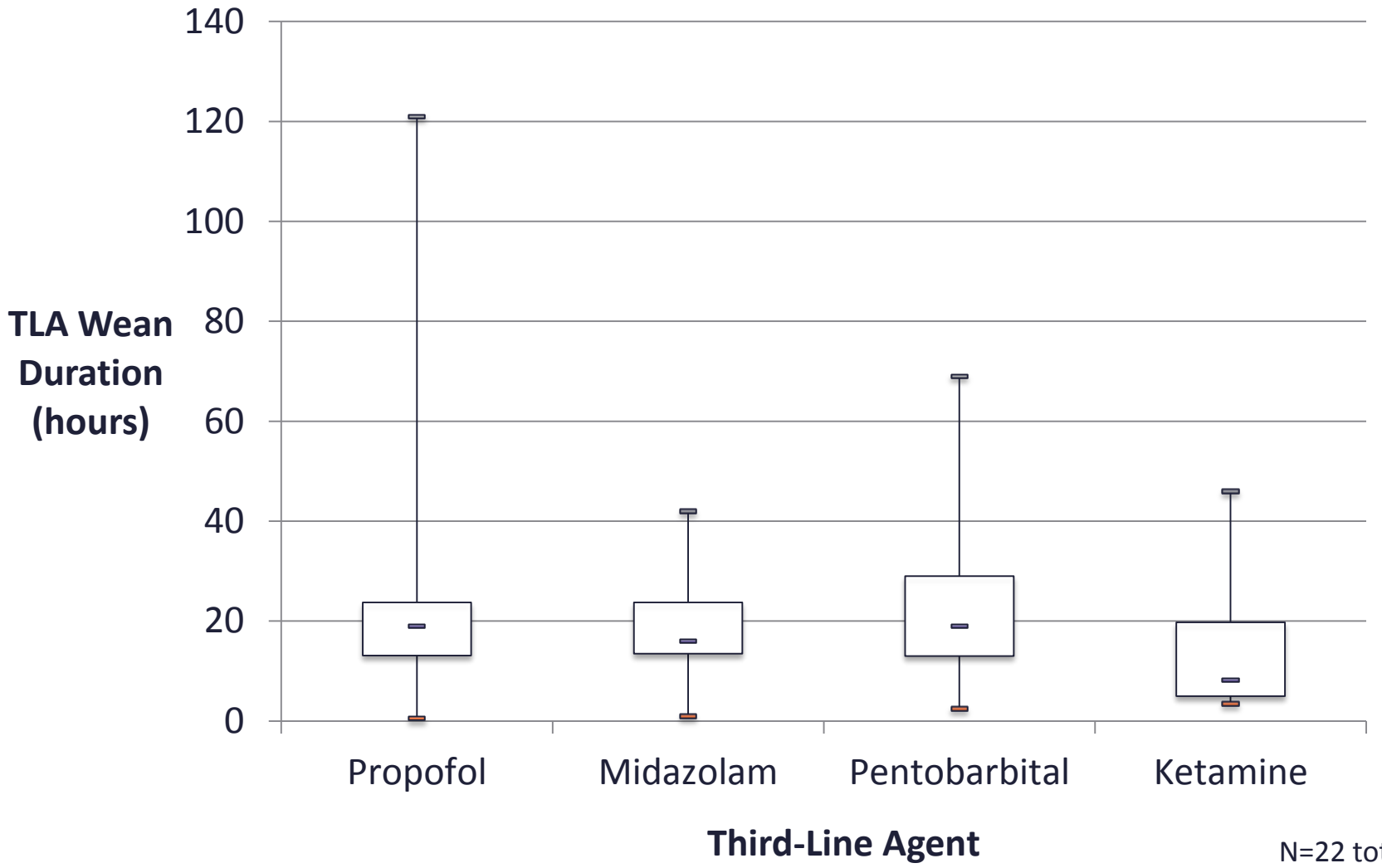


Endpoint I: wean of TLA prior to end of SAGE-547 maintenance

N=22 total evaluable patients

SRSE Phase 1/2 Clinical Observations

TLA Dosing Wean Duration

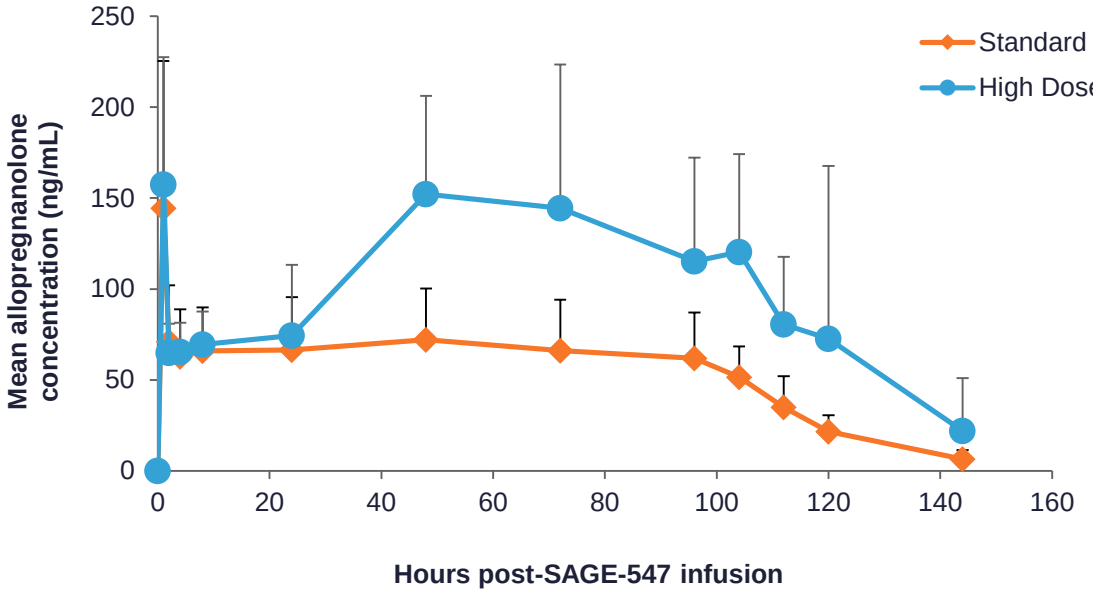


N=22 total evaluable patients

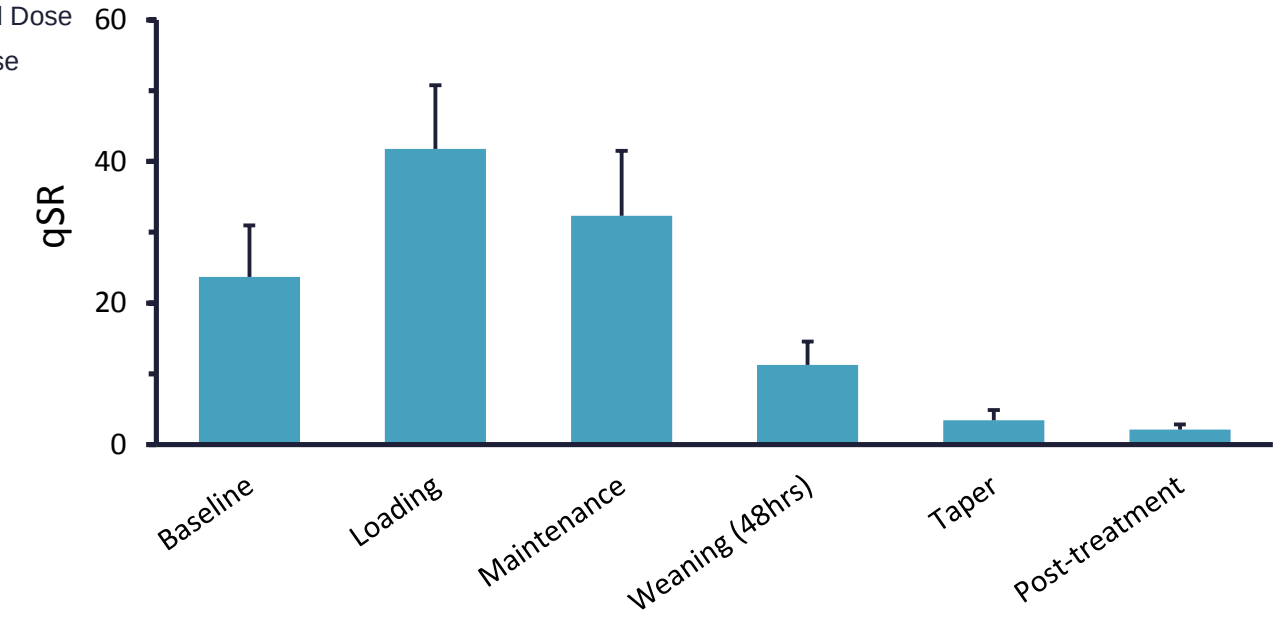
SRSE Phase 1/2 Clinical Observations

Pharmacokinetics and Exploratory EEG Biomarker

Well-Behaved Pharmacokinetics – Standard Dose Selected for Phase 3[1]



Dose-dependent and Pharmacodynamic Effects on EEG Suppression Ratio (qSR)[2]



- Examination of qSR through the SAGE-547 treatment period revealed highest levels of suppression during the loading and maintenance phases

1. Colquhoun et al, Neurocritical Care Society Annual Meeting, 2016; 2. Rosenthal et al, American Academy of Neurology Annual Meeting, 2016.

Phase 1/2 Safety Summary

Adverse Events (over 10%)	n (%)
Pyrexia	5 (20%)
Anaemia	4 (16%)
Blood urea increased	4 (16%)
Diarrhoea	4 (16%)
Hypotension	4 (16%)
Oedema peripheral	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 8%)	n (%)
Respiratory failure	3 (12%)
Convulsion	2 (8%)
Pulmonary embolism	2 (8%)
Renal failure acute	2 (8%)
Sepsis	2 (8%)

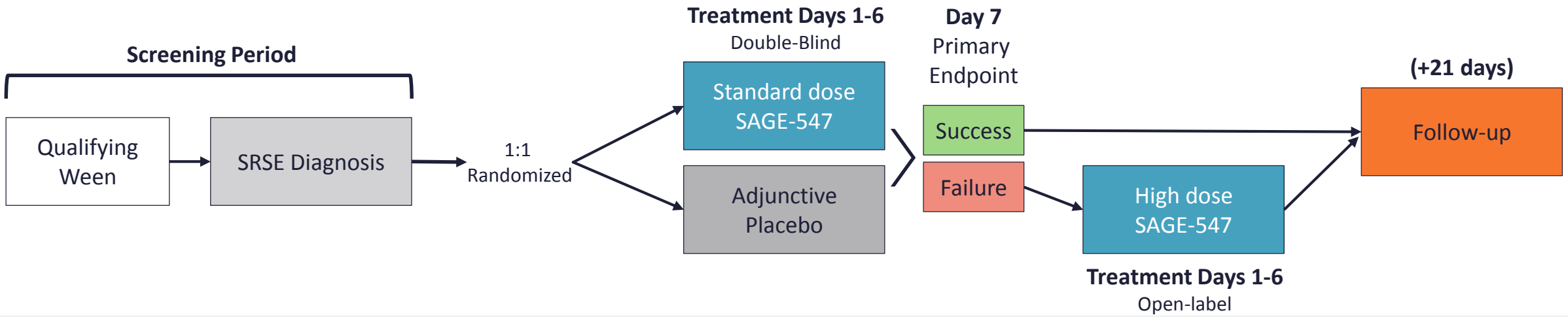
Cause of Deaths*	n
Respiratory failure or arrest	2
Cardiopulmonary arrest	1
Organophosphate toxicity	1
Metastatic breast cancer	1
Multi-organ failure	1

* None assessed as drug related by Sponsor

SAGE-547 Phase 3 SRSE Trial Design

STATUS TRIAL

- First-ever double-blind, placebo-controlled, randomized trial of a novel agent in SRSE
- Expect up to 140 patients enrolled to get 126 evaluable patients
- ~150 international sites (U.S., Canada, E.U., Israel)
- FDA Special Protocol Assessment and EMA Scientific Advice
- Primary Endpoint: continued resolution of SE for 24 hours following wean of all 3rd-line agents and SAGE-547/placebo



Phase 3 Anticipated Challenges

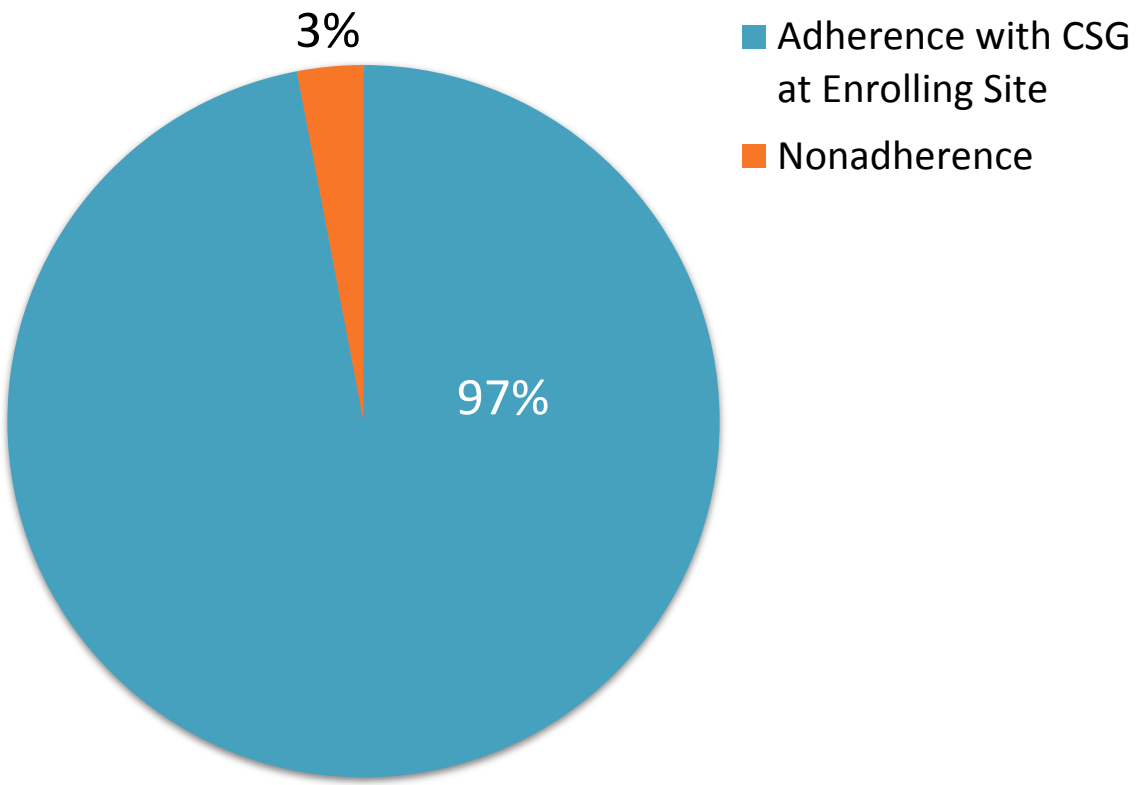
- **Challenge: Population heterogeneity**
- **Solution: Careful inclusion/exclusion criteria**
  - Qualifying ictal activity and medical monitor approval of all subjects prior to consent
  - Inclusion of adult and pediatric patients 2 years and older
  - Exclusion of SRSE attributed to hypoxic/anoxic encephalopathy with malignant EEG features

- **Challenge: Variability in underlying clinical treatment**
- **Solution: Clinical Standardization Guidelines (CSG)**
  - Definitions of ictal activity and anesthetic control
  - Guidance for IIC pattern management during anesthetic weaning

- **Challenge: Quality control across numerous sites**
- **Solution: Clinical Standardization Team (CST)**
  - Phone consultation with expert member
  - 24-7 availability
  - In-depth conversation for every subject documenting compliance

Phase 3 Clinical Trial Observation

Strong Adherence to Clinical Standardization Guidelines



(N=initial 125 call sample)

SAGE-547 in SRSE Summary

- The AE/SAE Phase 1/2 profile of SAGE-547 is consistent with historic SRSE populations
- Dose-dependent and pharmacodynamic effects on EEG suppression appear to be a biomarker independent of baseline anesthetics
- The +70% observed overall response rate in Phase 1/2 is high for a SRSE population:
  - SRSE termination is an achievable endpoint in a severe, heterogeneous population
- A SRSE clinical trial employing Clinical Standardization Guideline (CSG) oversight is a large undertaking, but…
  - A model structure for on-demand physician-to-physician communication is feasible despite time demands
  - CSG can be widely accepted and successfully implemented in the setting of a clinical trial
- Critical features are:
  - A large network of high-level epilepsy centers
  - A large-scale, expert, highly collaborative, and available clinical research organization and clinical standardization team

SAGE-547 in PPD

Samantha Meltzer-Brody, MD, MPH - UNC

Postpartum Depression is Common, Morbid & Often Missed

Common	Morbid	Missed	Heterogeneous
10-20% Prevalence	Devastating Consequences	Inconsistent Use of Practice Guidelines & Routine Screening	Timing of Onset
Most common unrecognized complication of perinatal period	Low Maternal Weight Gain Pre-term Birth	Symptoms often different from "Classic DSM Depression"	Symptom Presentation
	Impaired Attachment		
	Increase Risk: Suicide Infanticide		

Distinguishing Characteristics of Perinatal Mood Symptoms

- Anxiety or agitation
- Depressed mood
- Sadness, weepiness
- Irritability
- Hypervigilance about the baby
- OR lack of interest in the newborn
- Impaired concentration or feeling overwhelmed
- Feelings of dependency or guilt

Heritability of Perinatal Depression and Genetic Overlap With Nonperinatal Depression

Alexander Viktorin, M.Sc., Samantha Meltzer-Brody, M.D., M.P.H., Ralf Kuja-Halkola, Ph.D., Patrick F. Sullivan, M.D., F.R.A.N.Z.C.P., Mikael Landén, M.D., Ph.D., Paul Lichtenstein, Ph.D., Patrik K.E. Magnusson, Ph.D.

Objective: The authors investigated the relative importance of genetic and environmental influences on perinatal depression, and the genetic overlap between perinatal depression and nonperinatal depression.

Method: Analyses were conducted using structural equation modeling for 1) the lifetime version of the Edinburgh Postnatal Depression Scale in 3,427 Swedish female twins and 2) clinical diagnoses of depression separated into perinatal depression and nonperinatal depression in a Swedish population-based cohort of 580,006 sisters.

Results: In the twin study, the heritability of perinatal depression was estimated at 54% (95% CI=35%–70%), with the remaining variance attributable to nonshared environment (46%; 95% CI=31%–65%). In the sibling design, the heritability of perinatal depression was estimated at 44% (95% CI=35%–52%) and the heritability of nonperinatal depression at 32% (95% CI=24%–41%). Bivariate analysis showed that 14% of the total variance (or 33% of the genetic variance) in perinatal depression was unique for perinatal depression.

Conclusions: The heritability of perinatal depression was estimated at 54% and 44%, respectively, in separate samples, and the heritability of nonperinatal depression at 32%. One-third of the genetic contribution was unique to perinatal depression and not shared with nonperinatal depression, suggesting only partially overlapping genetic etiologies for perinatal depression and nonperinatal depression. The authors suggest that perinatal depression constitutes a subset of depression that could be prioritized for genomic discovery efforts. The study findings have direct translational impact that can assist clinicians in the counseling of their patients regarding risk and prognosis of perinatal depression.

AJP in Advance (doi: 10.1176/appi.ajp.2015.15010085)

Consequences of Untreated PPD

- Consistently associated with preterm birth
- Decreased breastfeeding initiation
- Increased risk of postpartum depression in future pregnancies
- SES, social support, marital status and h/o adversity
- Fetal effects--hyperactivity, irregular fetal heart rate
- Newborn effects:
  - Increased cortisol and norepinephrine levels
  - Decreased dopamine levels
  - Altered EEG patterns
  - Reduced vagal tone
  - Stress/depressive-like behaviors
  - Increased rates of premature deaths and neonatal intensive care unit admission

Sources: Grigoriadis S, *J Clin Psych*, 2013; Gaillard A, *Psychiatry Research*, 2014; Roomruangwong C, *Psychiatry Research*, 2016; Gentile S, *Neuroscience*, 2015.

Current Standard of Care for PPD Treatment

Routine Screening

- The postpartum period is one of the highest risk times for onset of a depressive episode

Psychotherapy

- Considered first line treatment for mild-moderate symptoms

Pharmacologic Treatment

- Must consider risk of medication exposure during lactation and impact of sleep deprivation
- SSRIs are first-line agents for pharmacologic PPD treatment
- Sertraline is often used due to favorable profile during lactation
- **However, evidence for their efficacy in PPD is limited**

Sources: Austin et al, *Women and Birth*, 2013; Kim et al, *Expert Opin Pharmacother,* 2014.

Evidence Based Protocol for Antidepressant Use in Postpartum Women who are Breastfeeding

BREASTFEEDING MEDICINE

Mary Ann Liebert, Inc. publishers

Journals | Search | Alerts

Breastfeed Med. 2015 Jul 1; 10(6): 290–299.

PMCID: PMC4523038

doi: 10.1089/bfm.2015.29002

ABM Clinical Protocol #18: Use of Antidepressants in Breastfeeding Mothers

Natasha K. Sriraman,[1] Kathryn Melvin,[2] and Samantha Meltzer-Brody[2,,3]

[1]Department of Pediatrics, Children's Hospital of The King's Daughters/Eastern Virginia Medical School, Norfolk, Virginia.
[2]Department of Psychiatry, University of North Carolina Chapel Hill School of Medicine, Chapel Hill, North Carolina.
[3]Perinatal Psychiatry Program, University of North Carolina Chapel Hill Center for Women's Mood Disorders, Chapel Hill, North Carolina.

the Academy of Breastfeeding Medicine

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Breastfeed Med

SAGE THERAPEUTICS

Increased Push in U.S. to Screen all Perinatal Women for PPD

HEALTH

Panel Calls for Depression Screenings During and After Pregnancy

By PAM BELLUCK JAN. 26, 2016

Women should be screened for depression during pregnancy and after giving birth, an influential government-appointed health panel said Tuesday, the first time it has recommended screening for maternal mental illness.

There is a Great Need for Novel Treatments in PPD

- Although SSRIs are commonly used as first-line PPD treatment, there is limited evidence for their use in the postpartum period specifically[1]

- The proportion of PPD patients treated successfully with SSRIs has a wide range (43%-88%)[2]

- Considering the unique pathophysiology of depression in the perinatal period and the negative consequences of untreated symptoms, **development of efficacious new treatments with more targeted mechanisms of action is warranted**

Sources: Kim et al, *Expert Opin Pharmacother,* 2014; De Crescenzo et al, *J Affect Disord*, 2014.

Dec 7, 2016: Congress Passes Health Bill with PPD Coverage

Congress Passes Groundbreaking Postpartum Depression Legislation

"Our moms need to know they matter."

12/07/2016 04:53 pm ET | **Updated** 4 hours ago

Over 400,000 women in the U.S. suffer from postpartum depression each year. Yet only an estimated 15 percent of those mothers receive treatment, and countless women who have suffered from PPD report feeling deeply alone in their struggles.

But the federal government is offering families a glimmer of hope for the future of maternal mental health in the U.S.

Normal Changes in the HPA Axis During Pregnancy and into the Postpartum Period

3rd Trimester	Childbirth & During Transition to Postpartum Period
High estrogen and progesterone levels	Rapidly declining estrogen and progesterone
Hyperactive HPA axis with high plasma cortisol	Blunted HPA axis activity due to suppressed hypothalamic CRH secretion

The Role of Allopregnanolone in PPD

ALLO Levels:

In animal studies, ALLO has been shown to modulate biological processes that are dysregulated in major depressive disorder :

- HPA Axis Regulation[2]
- Neuroprotection[3]
- Immune Function[4]

In animal studies, ALLO has been shown to regulate the neural circuits that are implicated in depression, including the limbic system[5]

[1] Schüle C, 2007
[2] Barbaccia, ML, 1997
[3] Djebaili, M, 2005
[4] He, J, 2004
[5] Akwa, Y, 1999

Allopregnanolone in Postpartum Period

Studies suggest that, even in the presence of normal absolute levels, **perinatal fluctuations in reproductive hormones may precipitate symptoms** in a vulnerable subpopulation of women as a result of changing ALLO levels.

- Cortical GABA and ALLO are reduced in postpartum women, compared with healthy women in the follicular phase[1]
- Women with PPD show reduced resting state functional connectivity between the anterior cingulate cortex, amygdala, hippocampus, and dorsolateral prefrontal cortex in the context of the postnatal decline in ALLO[2]
- Association of changes in ALLO levels and depressive symptoms during GnRH agonist-induced ovarian suppression and ovarian steroid addback in women with a history of PPD, but not in those without such a history[3]

[1] Epperson CN 2006
[2] Deligiannidis KM, 2013
[3] Schiller CE 2014

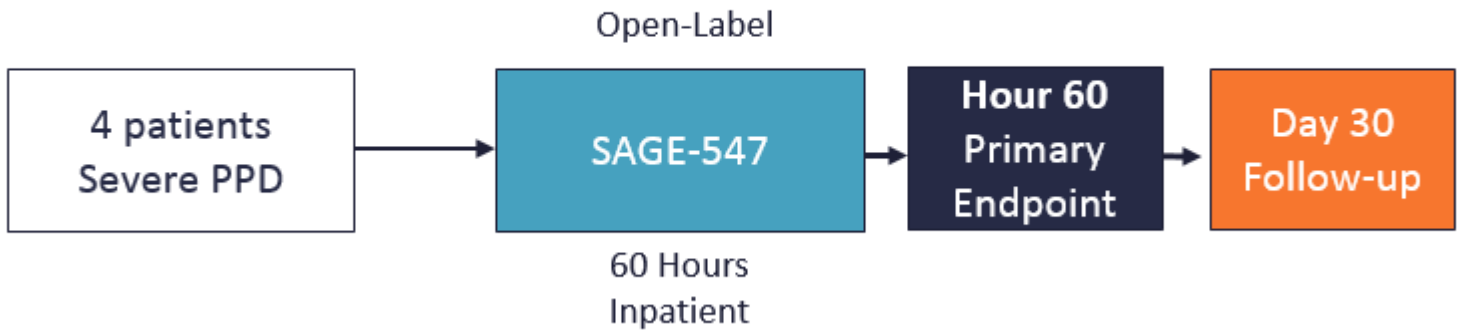
SAGE-547 in PPD

Study 201: Open-Label Proof-of-Concept

Study Population	Key Endpoints

- 4 patients diagnosed with severe PPD
- Major depressive episode in 3rd trimester or within 4 weeks post-birth
- HAM-D ≥26
- Stable background therapy allowed

- Change from baseline in HAM-D total score
- Safety, tolerability and pharmacokinetics

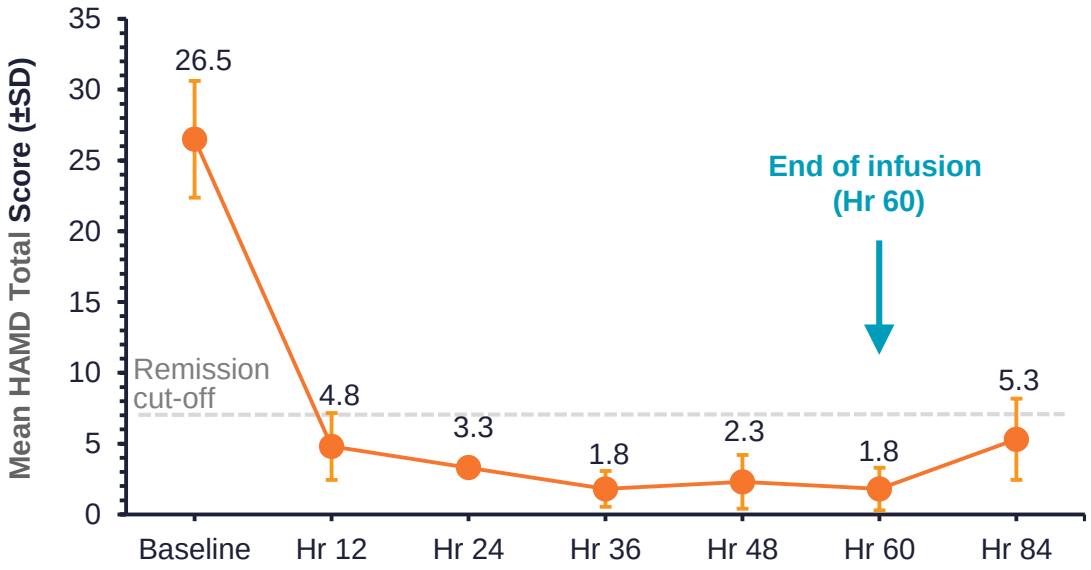


SAGE-547 in PPD

Positive Study 201 Results

- 4/4 patients achieved remission and significant improvement of mean Hamilton Rating Scale for Depression (HAM-D) scores
- No SAEs observed during 30 day follow-up: only AE reported in more than 1 patient was sedation (2 patients)

Mean HAMD Total Score Over Time



Other Efficacy Assessments

	Baseline	Hr 12	Hr 24	Hr 36	Hr 48	Hr 60	Hr 84
CGI-I	-	1.8	1.3	1.0	1.3	1.3	1.5
EPDS	18.6	-	4.3	3.3	2.0	2.8	2.8
GAD-7	12.5	-	1.0	0.3	1.3	0.8	0.8
PHQ-9	15.8	-	1.8	1.5	1.3	1.3	2.0

CGI-I: Clinical Global Impression-Improvement. EPDS: Edinburgh Postnatal Depression Scale. GAD-7: 7-item Generalized Anxiety Disorder Scale. PHQ-9: Patient Health Questionnaire.

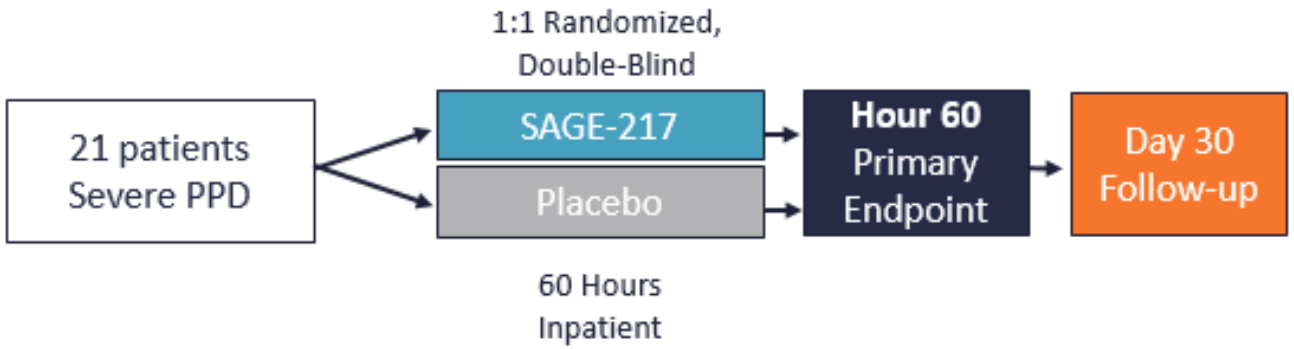
SAGE-547 in PPD

202A Study in Severe PPD

Study Population	Key Endpoints

- Placebo-controlled, double-blind 1:1 randomization
- Enrolled 21 patients (10 SAGE-547, 11 placebo)
- Major depressive episode in 3rd trimester or within 4 weeks post-birth
- HAM-D ≥26

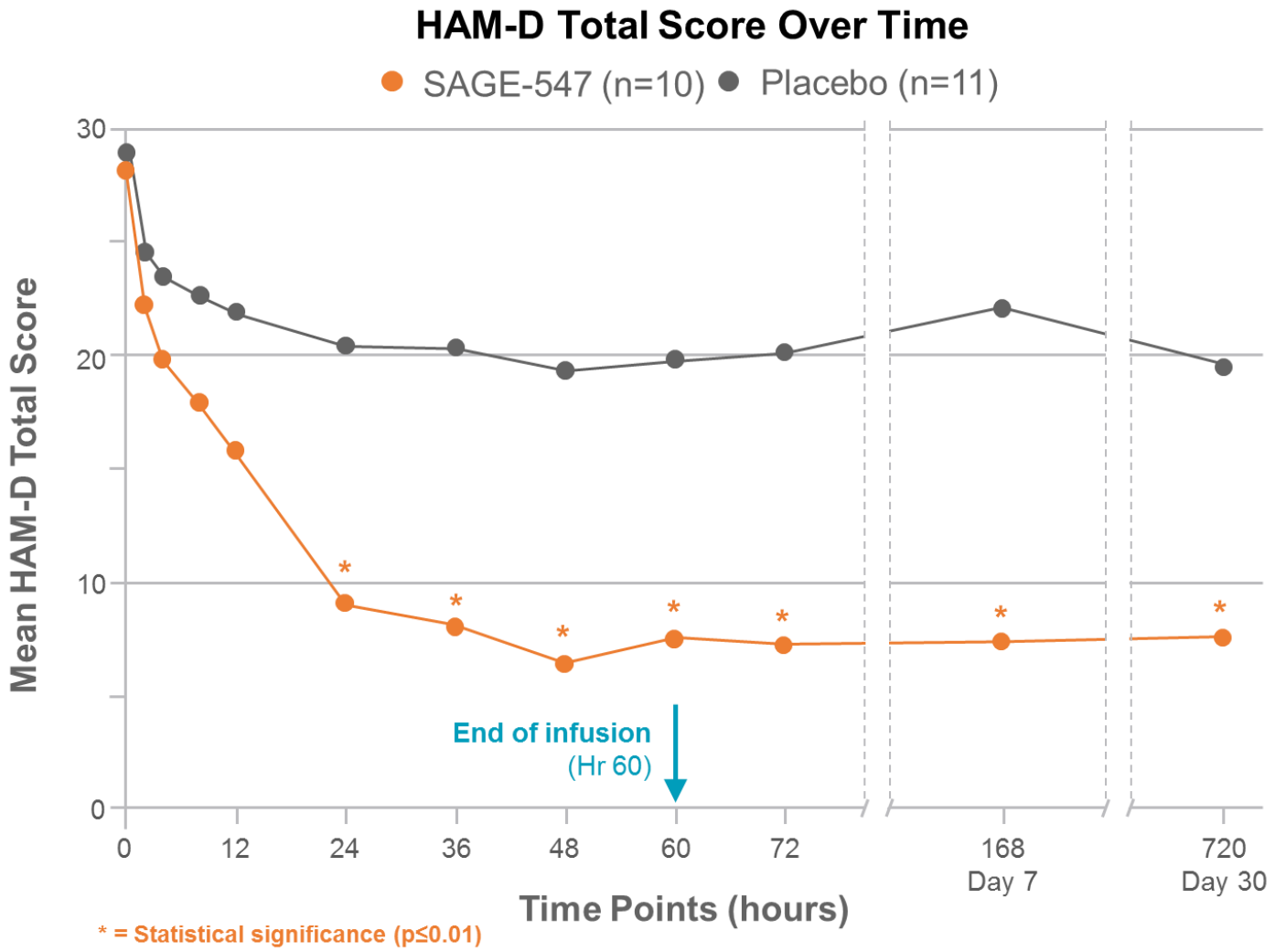
- Change from baseline in HAM-D total score at 60 hours compared to placebo
- Safety, tolerability and pharmacokinetics



SAGE-547 in PPD

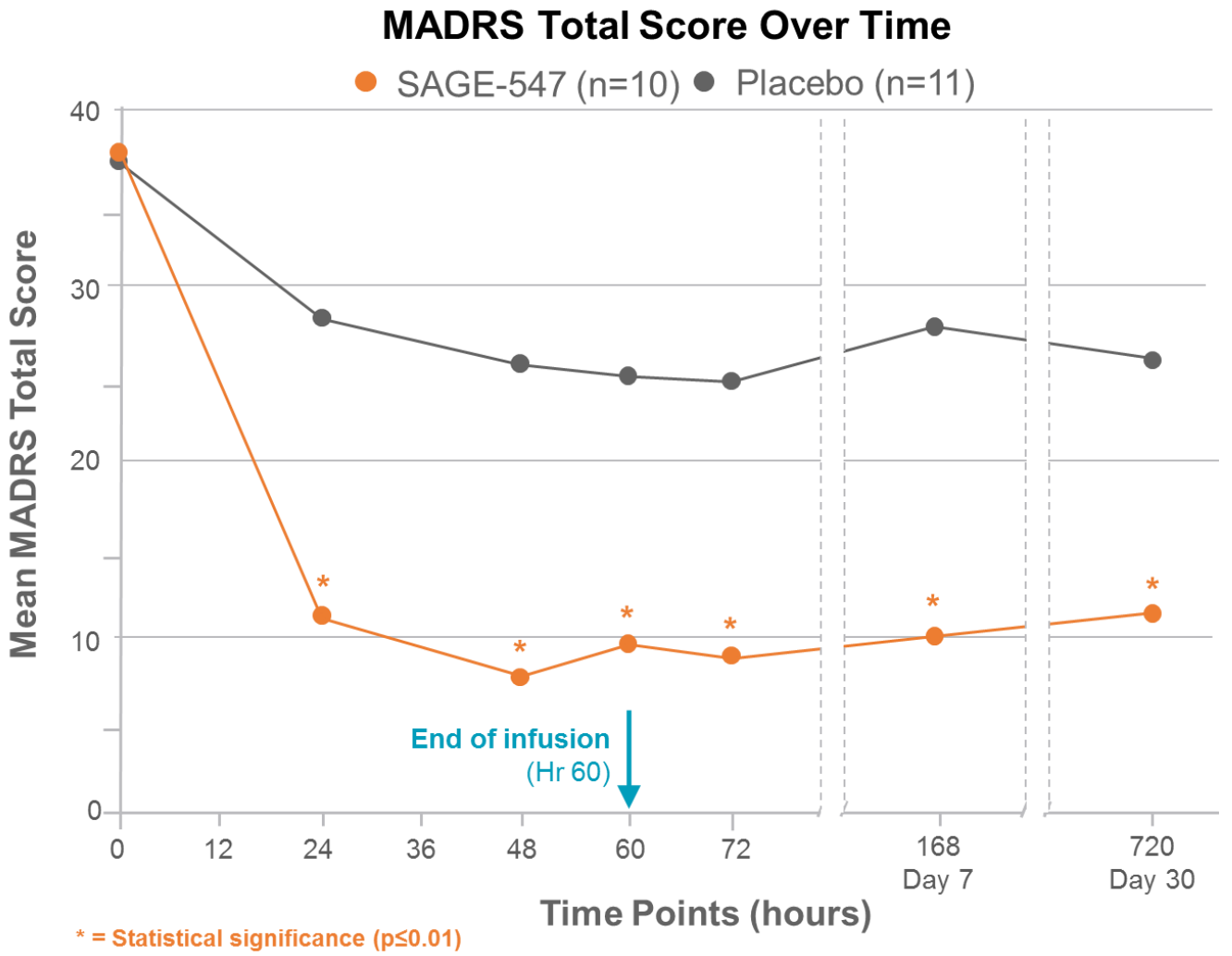
202A Results: Primary Analysis - SAGE-547 vs. Placebo HAM-D Efficacy Results

Primary Endpoint (p=0.008) at 60 hours



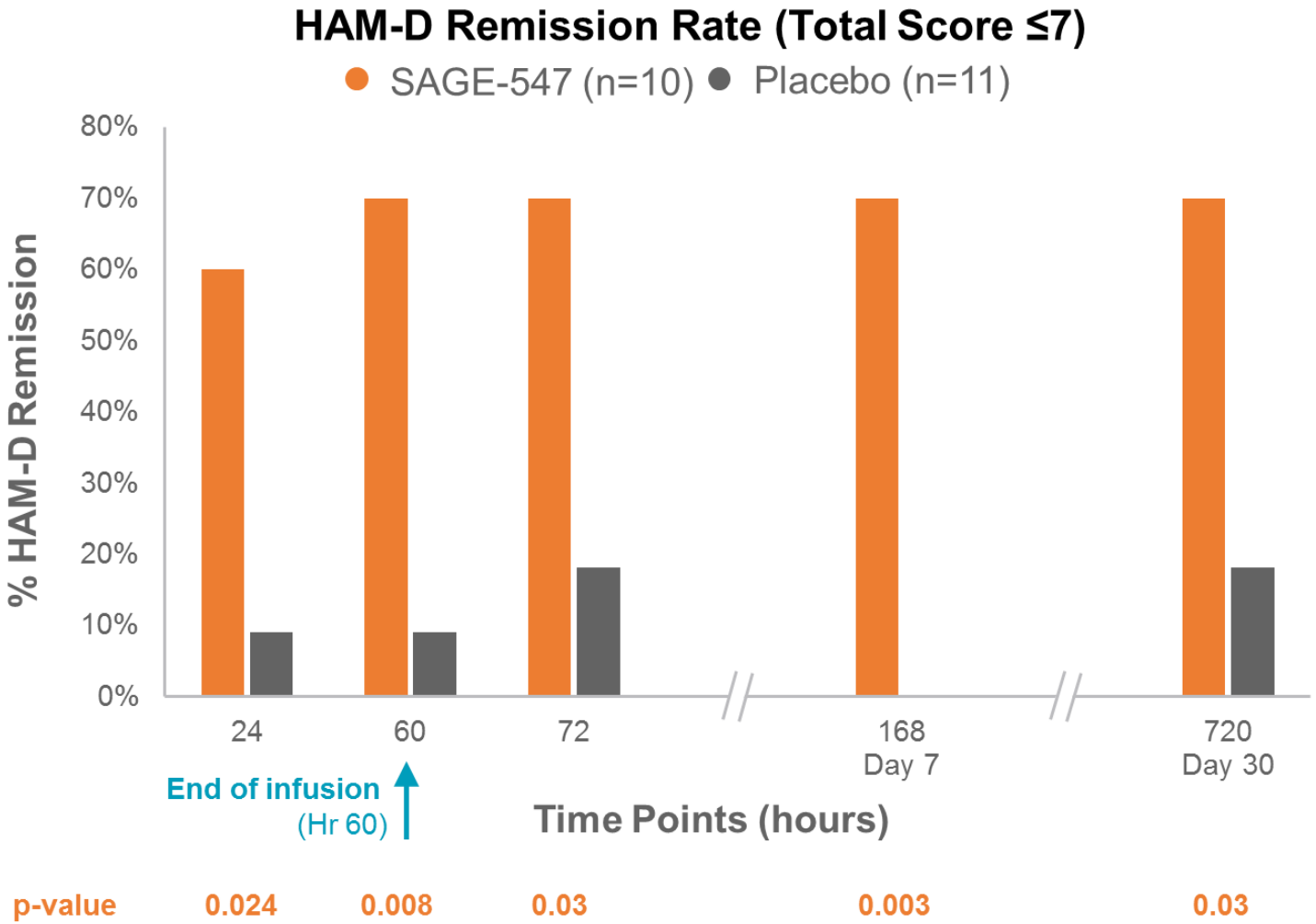
SAGE-547 in PPD

202A Results: Rapid and Sustained Improvement on MADRS



SAGE-547 in PPD

202A Results: SAGE-547 Remission Higher than Placebo at 24 Hours through 30 Days



SAGE-547 in PPD

202A Results: Safety and Tolerability Summary

- SAGE-547 was generally well tolerated
  - No deaths, SAEs or discontinuations due to adverse events (AEs)
- Fewer patients reported AEs on SAGE-547 vs. placebo:
  - SAGE-547 (4) vs. placebo (8)
- Similar numbers of patients reported Nervous System Disorder AEs
  - SAGE-547 (3) vs. placebo (4)
- Equal number of patients reported the cluster of Dizziness, Sedation or Somnolence
  - SAGE-547 (3) vs. placebo (3)
- Fewer SAGE-547 patients reported Psychiatric Disorder AEs
  - SAGE-547 (0) vs. placebo (5)
  - AEs included abnormal dreams, insomnia and anxiety for placebo

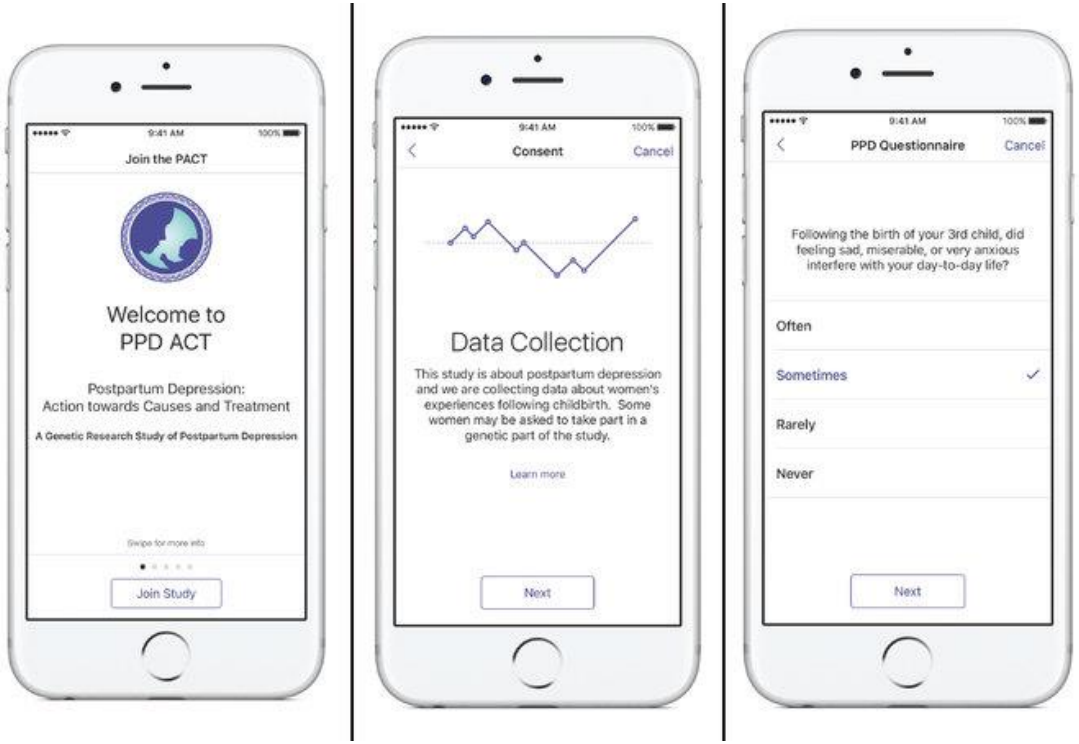
Conclusion

- Untreated PPD is associated with poor outcomes for mother, fetus, newborn and longer term impact in offspring
- Allopregnanolone plays an important role in the postpartum period
- Treatment of women with severe PPD with SAGE-547 in 202A resulted in rapid, significant, and sustained reductions in HAM-D total score when compared to placebo-treated patients
  - Statistically significant remission rates (HAM-D≤7) were observed for SAGE-547 treatment at 60 hours versus placebo treatment
  - Secondary efficacy measurements confirmed the primary, HAM-D-based endpoints
- SAGE-547 was generally well tolerated
  - Fewer patients reported AEs on SAGE-547 (4) compared with placebo (8)
- Important to develop targeted approaches for prospective identification and treatment

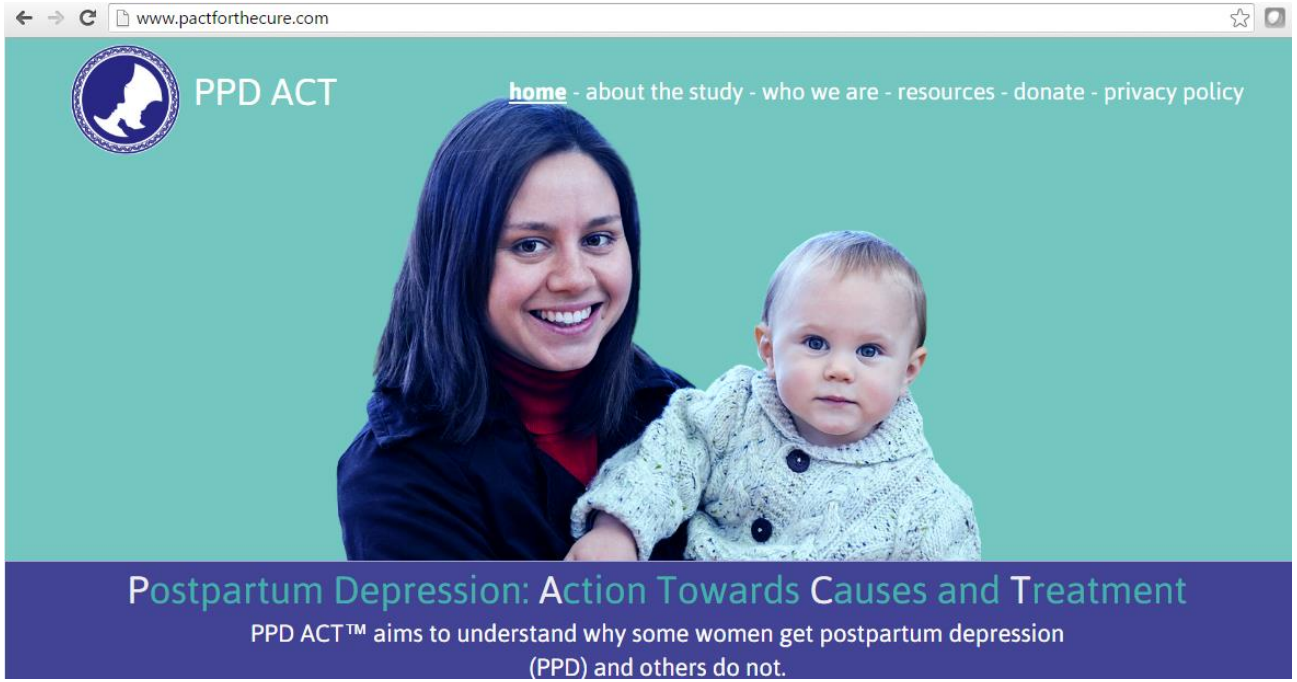
PPD ACT Study

Novel iPhone Study to Investigate Genetic Risks of PPD

- Launched March 2016 in partnership with Apple
- Purpose:
  - To understand why some women suffer from PPD and others do not
  - Aim to improve detection, prevention and treatment
- Study Description:
  - Survey delivered via app to identify women who have had symptoms of PPD
  - Eligible women invited to provide DNA samples
  - Goal to collect 100,000 DNA samples
- Highlights:
  - Informed consent built into the app
  - US and Australia (Canada and UK soon)
  - UNC IRB approved (US version)



Using Social Media to Recruit >12,000 women in 6 Months



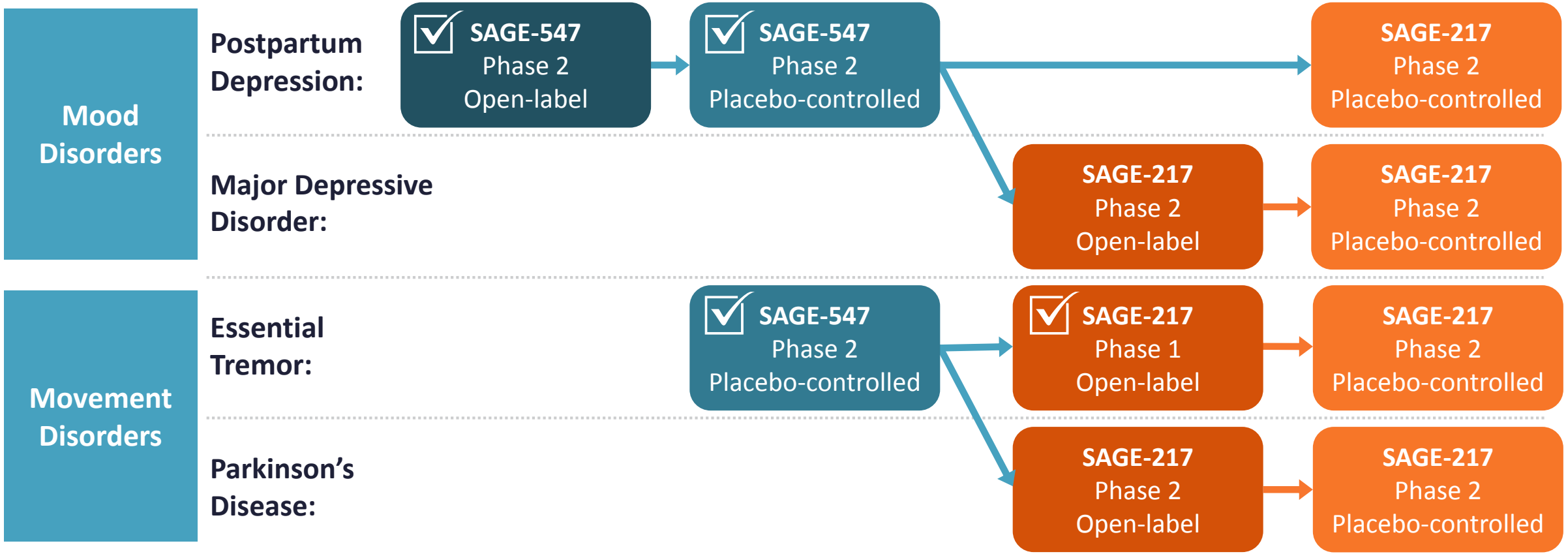
SAGE THERAPEUTICS™

SAGE-217: A First-in-Class Oral Modulator

Steve Kanes, MD, PhD - CMO

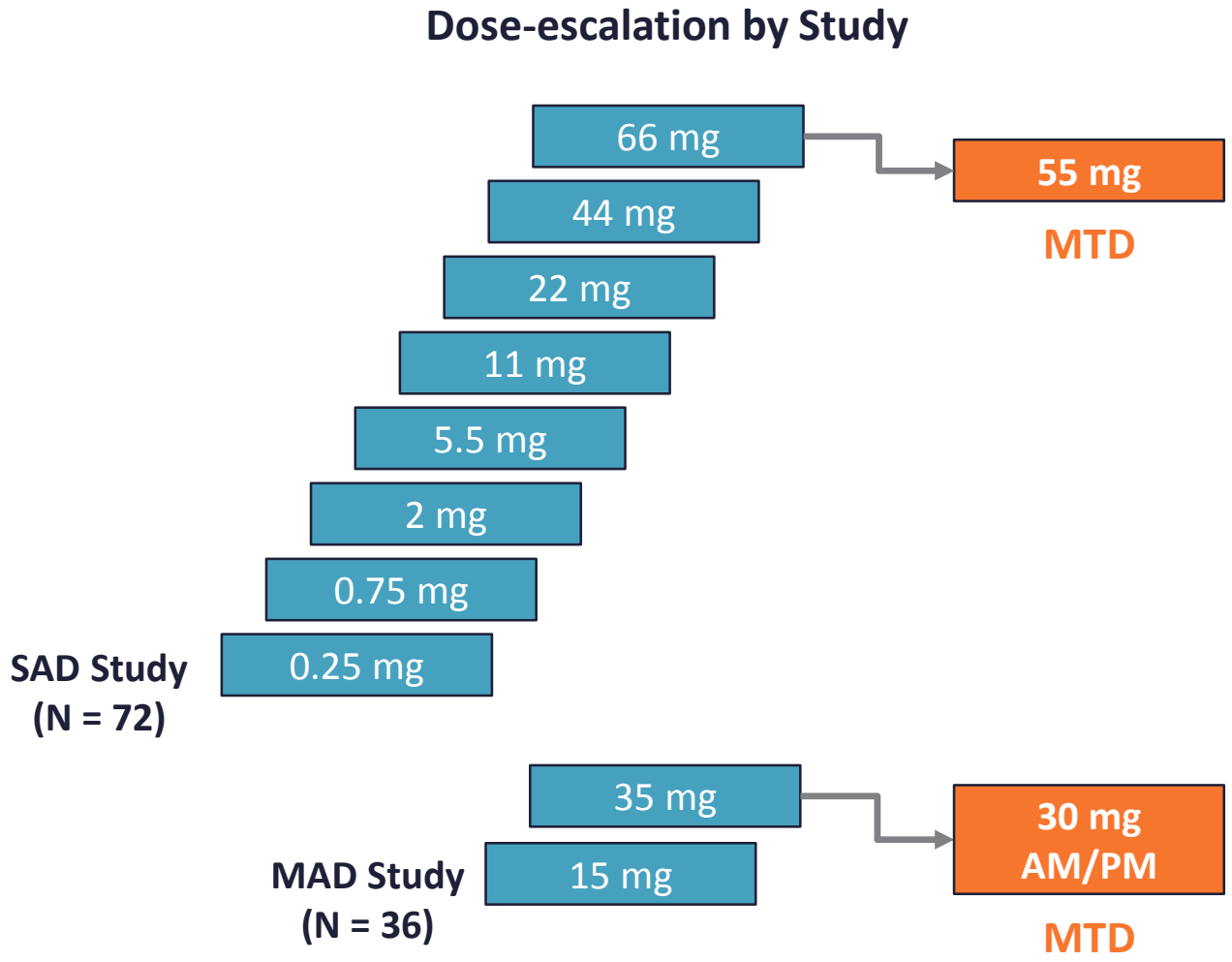
SAGE-217 Clinical Development Strategy

Positive Data Drive Incremental De-Risking



SAGE-217: Innovative Phase 1 Program

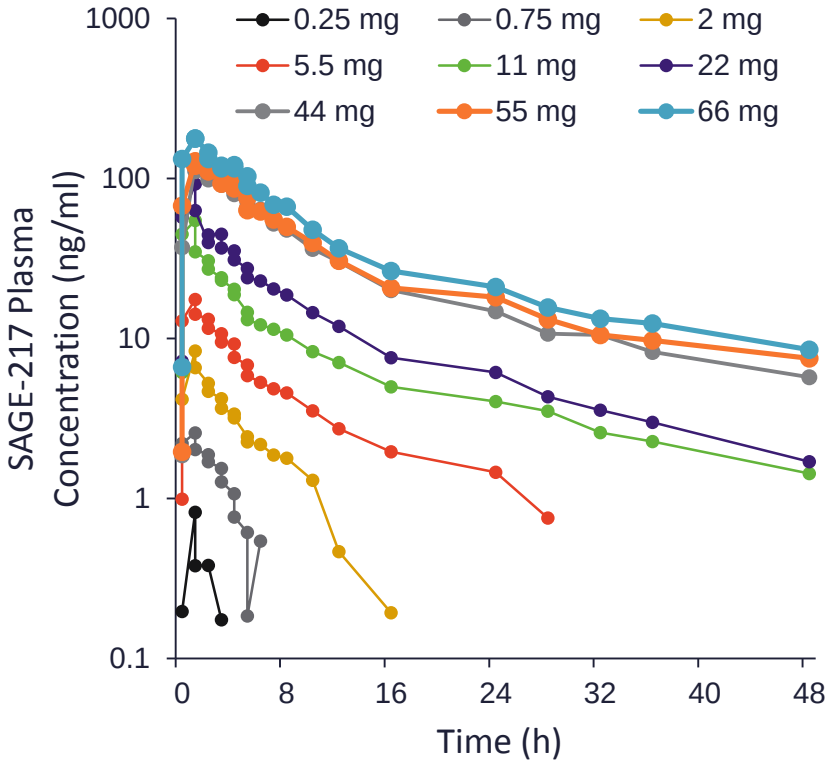
- Single (SAD) and multiple ascending dose (MAD) trials in 108 healthy volunteers
- Primary objectives to assess safety, tolerability, pharmacokinetics and CNS target engagement
- Evaluated AM/PM dosing, fasting and fed dosing, DDI, eye tracking, EEG, cognition and essential tremor open-label cohort



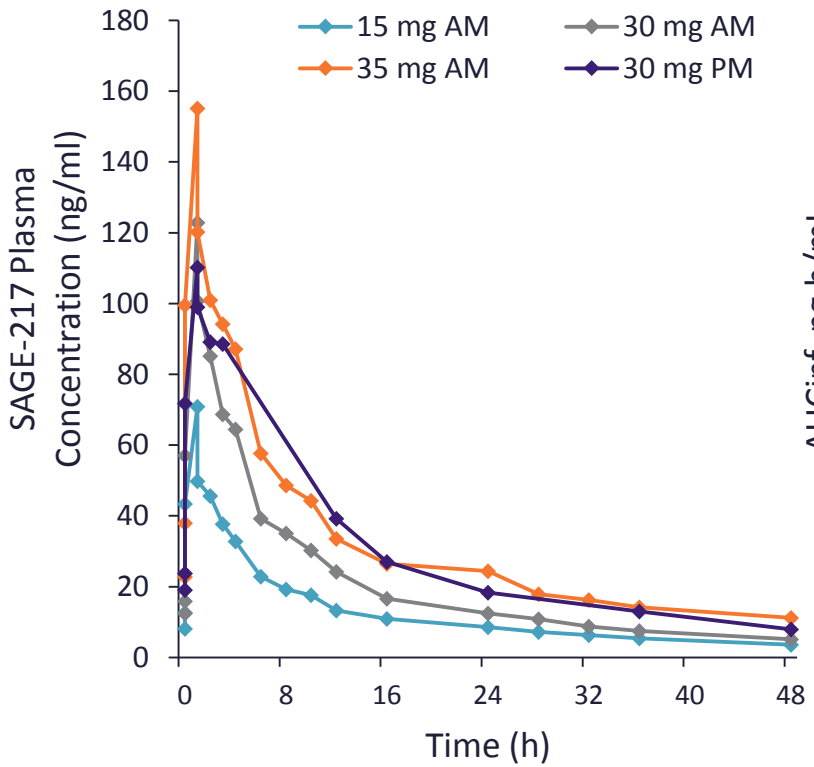
SAGE-217 Pharmacokinetics

Well-Behaved Molecule in 108 Subjects in Phase 1

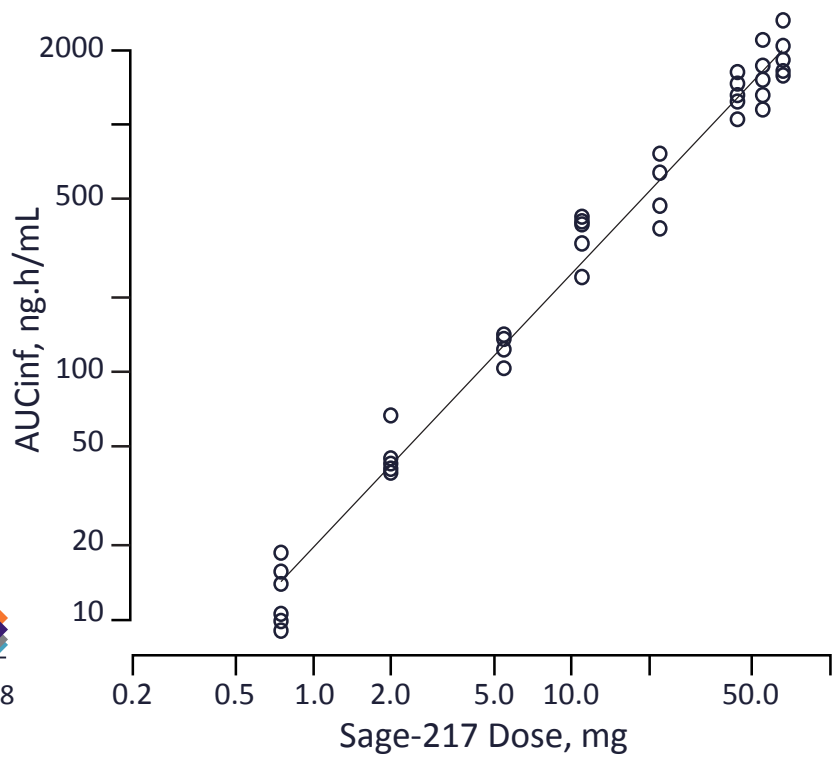
Mean Plasma Concentration v. Time (SAD)



Mean Plasma Concentration v. Time (MAD)



Dose Linearity Across SAD and MAD



SAGE-217 was orally bioavailable with half-life of 16-21 hours and Tmax ~1 hour

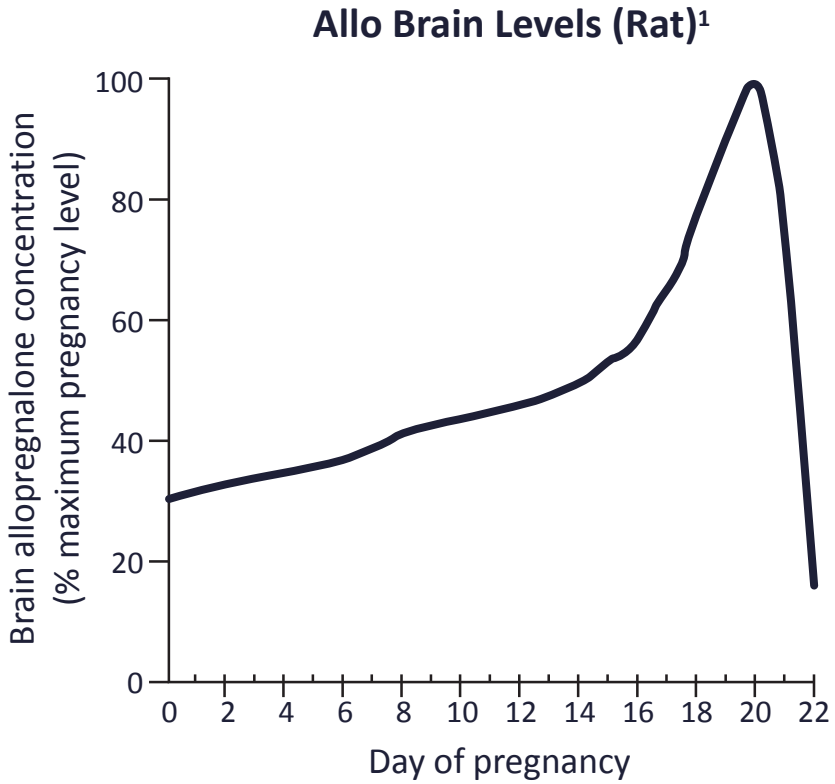
SAGE-217 Phase 1 Results

Supports Moving to Multiple Phase 2 Programs

- SAGE-217 generally well tolerated with no serious adverse events reported
  - Tolerability is consistent with preclinical profile
  - No significant effect on psychomotor and cognitive assessments
  - Rates of moderate to deep sedation (MOAA/S <3) were comparable to placebo until the maximum tolerated dose (MTD) was reached
- EEG showed clear evidence of target engagement ($GABA_A$ receptor modulation) starting at the lowest dose tested (15 mg)
- Plasma half-life consistent with once/day dosing (if desired)

Why Postpartum Depression?

Changes in Allopregnanolone During Pregnancy



Disease Overview

- Postpartum depression (PPD) is considered moderate-severe MDD in women who have recently given birth
- Current standard of care includes cautious use of antidepressants in nursing mothers
- There are no therapies specifically approved for PPD

Pathophysiology

- Changes in reproductive hormones during and after pregnancy have been closely linked to depressive symptoms and mood dysregulation[2]
- Women with PPD may have an impaired ability to regulate neuronal function, revealed during perinatal changes in hormone levels
- Trafficking of extrasynaptic $GABA_A$ receptors may become disrupted due to these changing levels[3]

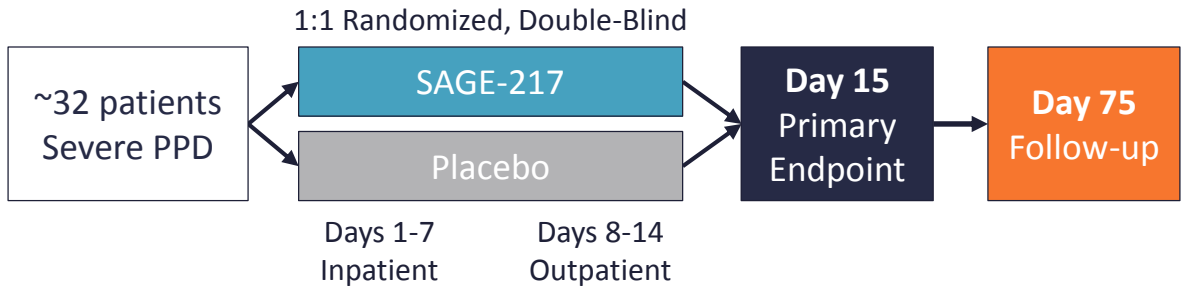
1. Brunton et al, *Progress in Neurobiology*, 2014; 2. Luscher et al, *Molecular Psychiatry*, 2011; 3. Maguire et al, *Journal of Neuroscience*, 2009.

SAGE-217 in PPD

Planned Phase 2 Program

Study Population	Key Endpoints
• ~32 patients diagnosed with severe PPD • Major depressive episode in 3rd trimester or within 4 weeks post-birth • HAM-D ≥26 • Stable background therapy allowed	• Change from baseline in HAM-D total score at Day 14 compared to placebo • Safety, tolerability and pharmacokinetics

NEST PROGRAM

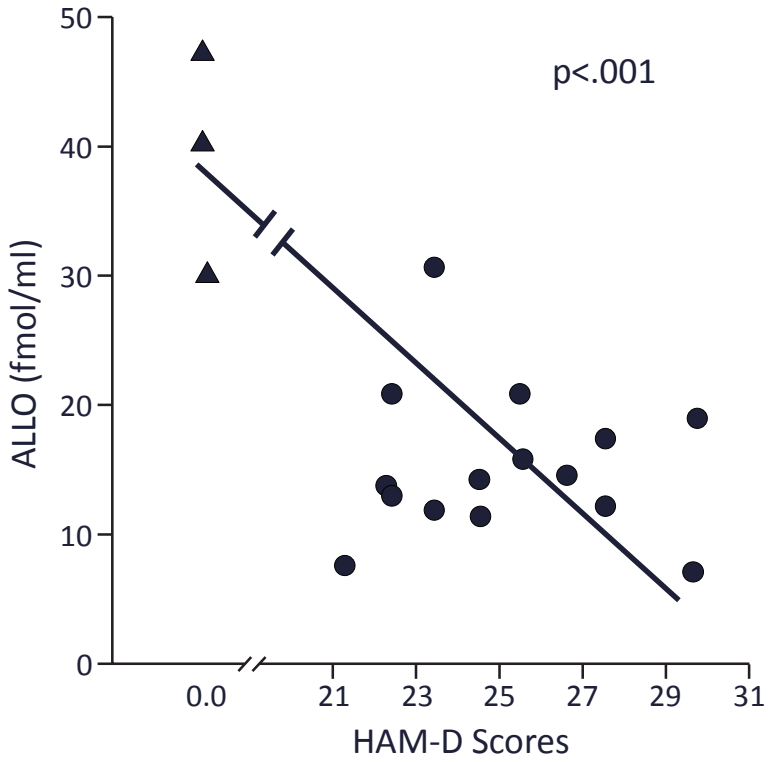


Developing SAGE-217 as a first-in-class oral $GABA_A$ modulator for PPD

Why Major Depressive Disorder?

Low Allopregnanolone Levels have Been Observed in MDD Patients

Allo CSF Levels Decrease with Severity[1]



Disease Overview

- Majority of patients may not adequately respond to initial antidepressant therapy
- Antidepressants are widely used, but large scale studies have demonstrated their limited efficacy

Pathophysiology

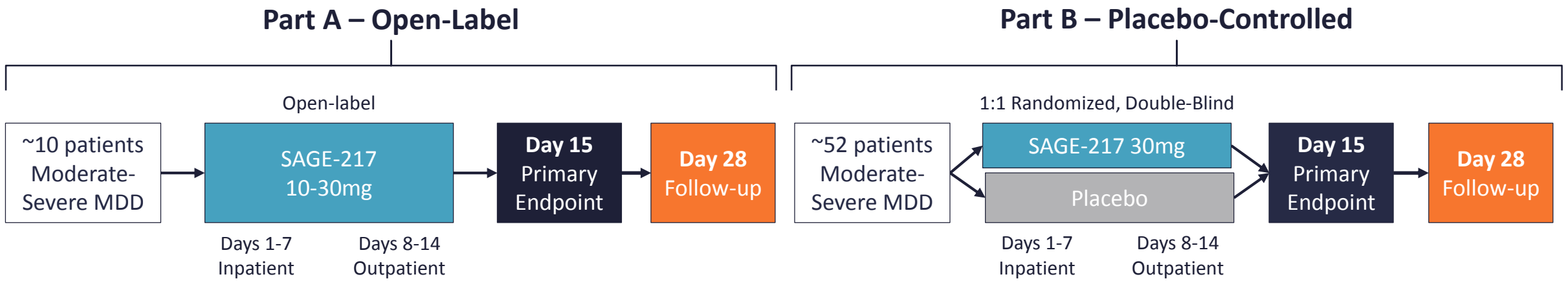
- Preclinical and clinical evidence suggest the role of GABAergic dysfunction in depression
- Low GABA and allopregnanolone levels have been found in the brain, CSF and plasma of depressed patients[2]
- Antidepressant therapy can restore allopregnanolone levels in animal models of depression[3]

1. Uzunova et al., *PNAS*, 1998; 2. Luscher et al, *Molecular Psychiatry*, 2011; 3. Schule et al, *Progress in Neurobiology*, 2014.

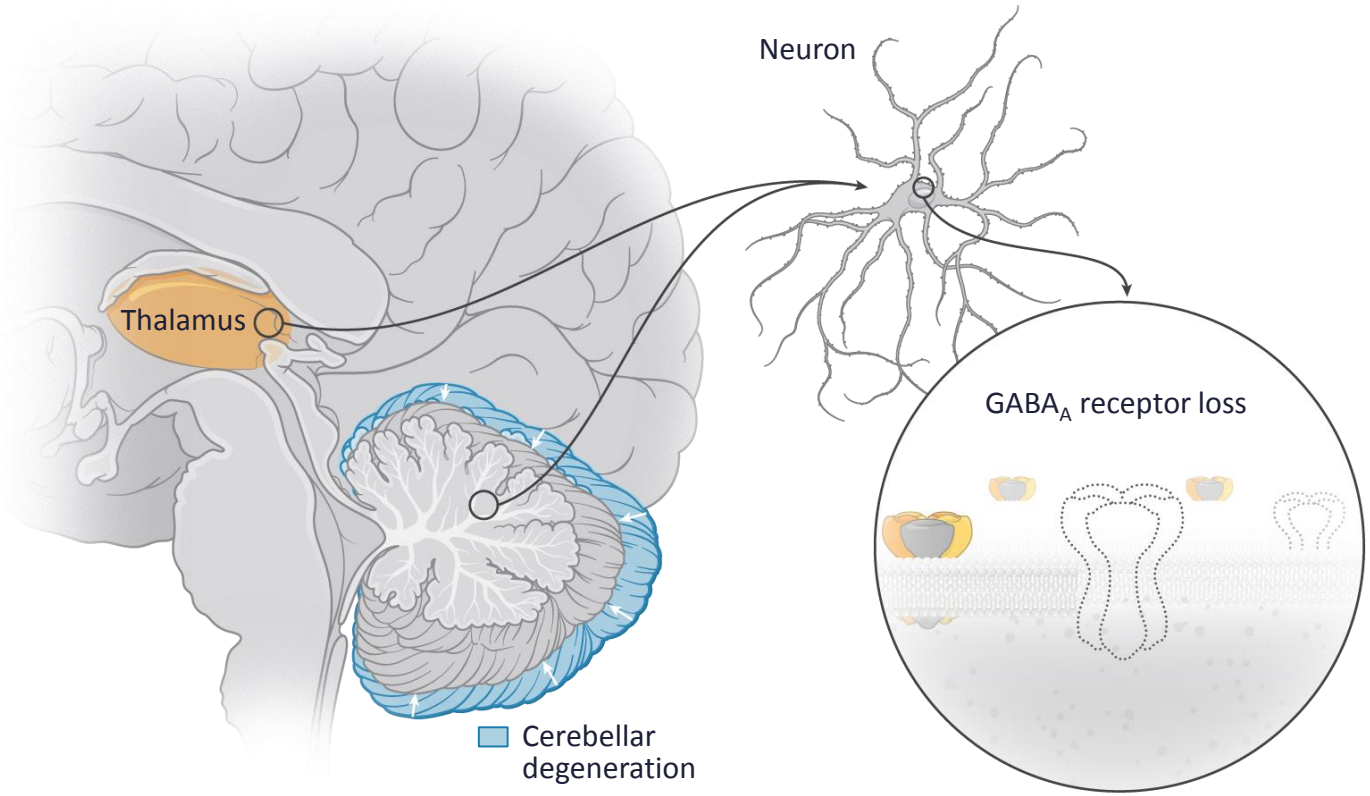
SAGE-217 in MDD

Planned Phase 2 Proof-of-Concept Program

Study Population	Key Endpoints
• Patients with MDD present for 4-week period • HAM-D ≥22; HAM-A ≥20 (Part B only) • ~10 patients (Part A); ~52 patients (Part B)	• Safety, tolerability and pharmacokinetics • Change from baseline in HAM-D total score



Why Essential Tremor ?



Disease Overview

- Essential tremor (ET) is the most prevalent movement disorder[1]
- Tremors may impede patients' ability to perform tasks or activities of daily living
- Current treatments include primidone and propranolol - existing treatments are ineffective in 30-50% of patients

Pathophysiology

- ET is associated with reduction in GABAergic tone in the cerebellum and thalamus, hypothesized to result from neurodegenerative changes[2]
- Reduced GABA levels have been measured in CSF in ET patients[3]
- Postmortem analysis of ET patients found reduction of 35% in GABA$_A$ receptors[2]

1. Louis ED, Ferreira JJ, *Movement Disorders*, 2010; 2. Paris-Robidas et al, *Brain*, 2012; 3. Mally et al, *J Neural Transm*, 1996.

SAGE-217 in Essential Tremor

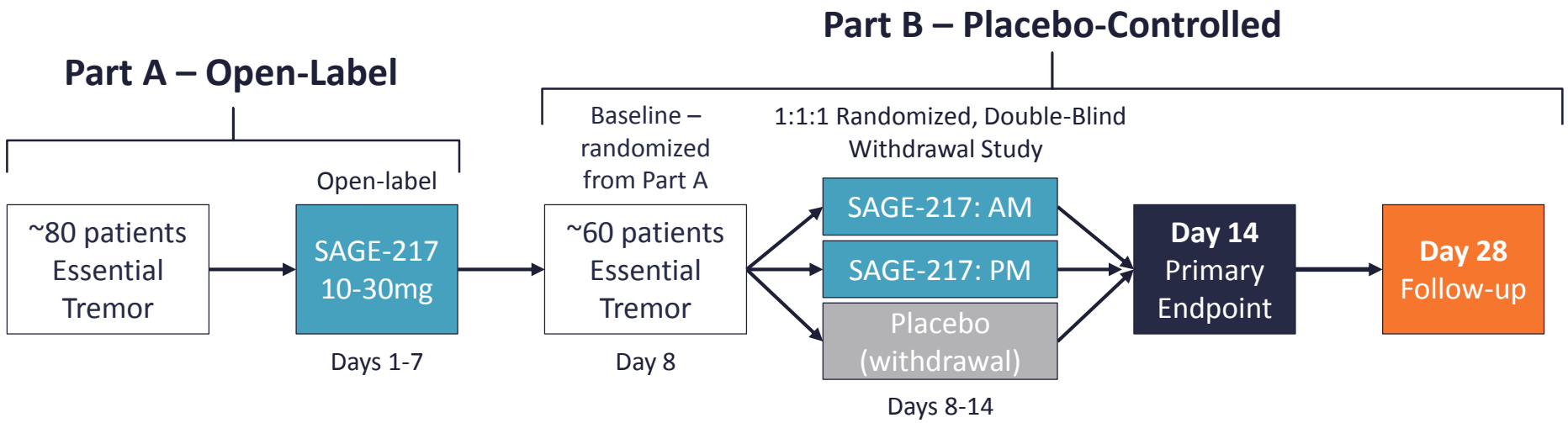
Planned Phase 2 Program

Study Population

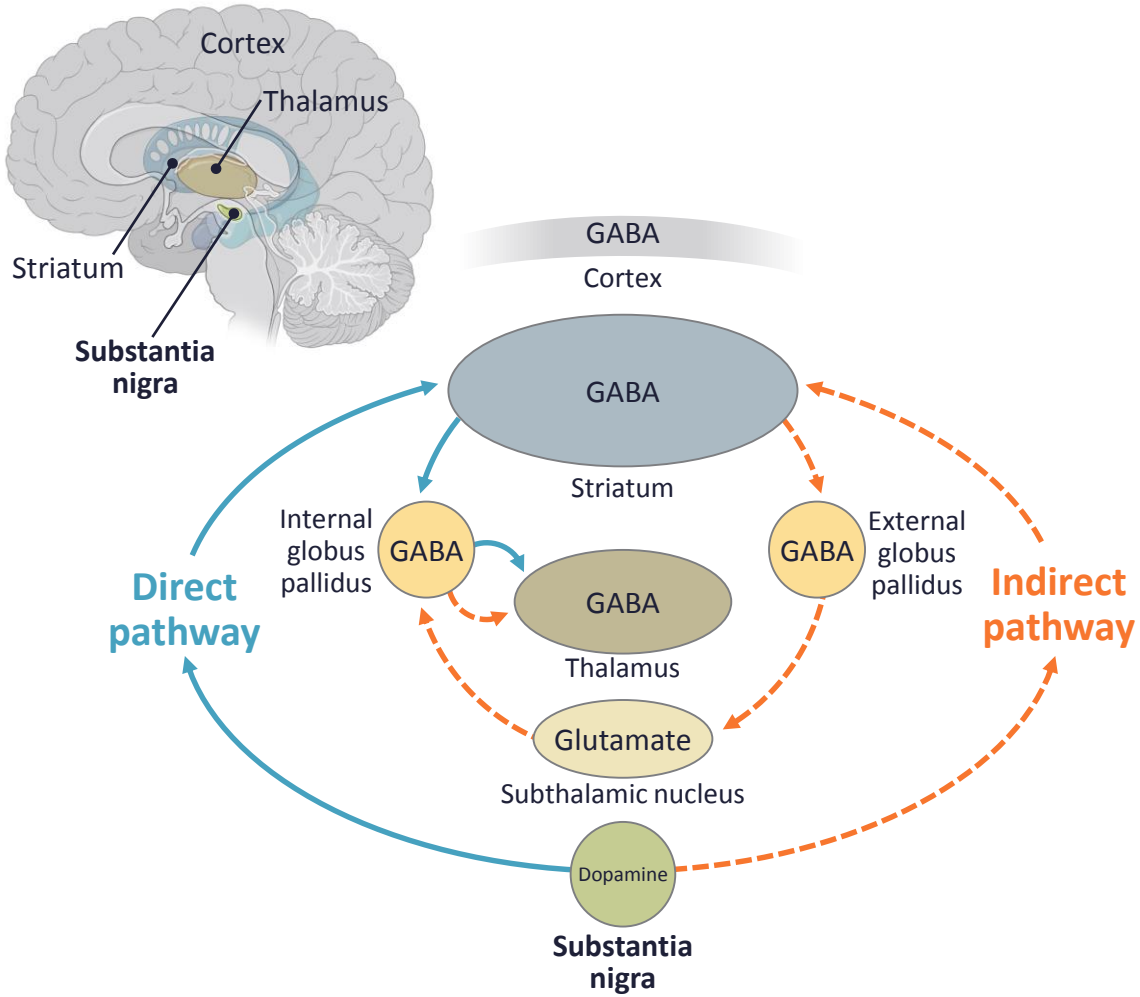
- Essential tremor patients with duration of >5 years
- ~80 patients (Part A); ~60 patients (Part B)
- To qualify for Part B: must have tolerated at least 10mg of SAGE-217 and shown 30% reduction in TETRAS kinetic tremor combined score

Key Endpoints

- Change from Day 8 randomization in Kinesia kinetic tremor combined score compared to placebo
- Safety, tolerability and pharmacokinetics



Why Parkinson's Disease?



Disease Overview

- Parkinson's disease (PD) is a neurodegenerative disorder with motor and non-motor symptoms, including resting tremor and mood disorders
- Current treatment consists of dopamine replacement (levodopa/carbidopa), however, treatment is associated with motor complications

Pathophysiology

- PD is associated with loss of dopaminergic cells in the substantia nigra and alteration of the basal ganglia circuitry[1]
- The substantia nigra produces high levels of allopregnanolone ($GABA_A$ modulator)[2]
- Dopamine neurons are under control of the GABA system
- Decreased levels of allopregnanolone have been measured in plasma and cerebrospinal fluids in PD patients[3]

1. Siderowf A, Lang AE, *Movement Disorders*, 2012; 2. di Michele et al, *Front Neuroendocrinol*, 2013; 3. di Michele et al, *Neurol Sci,* 2003.

SAGE-217 in Parkinson's Disease

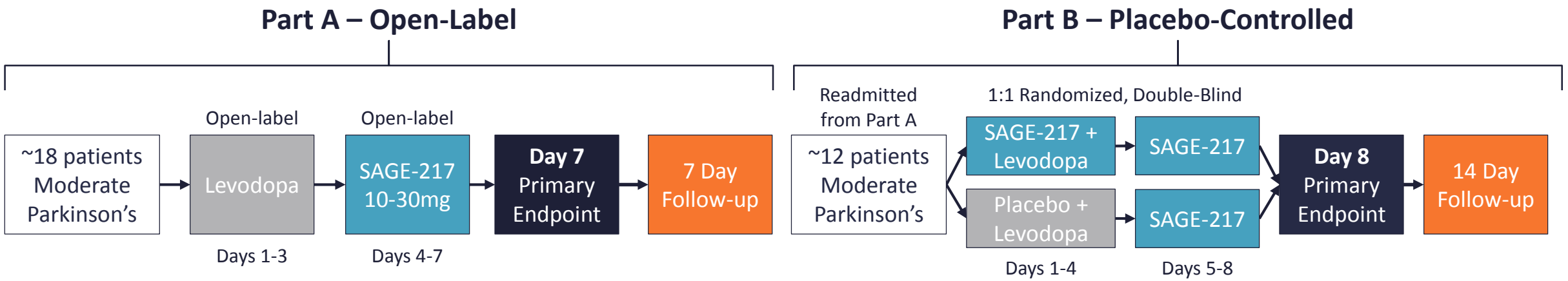
Planned Phase 2 Proof-of-Concept Program

Study Population

- PD patients with duration less than 7 years and moderate severity (stage 2 or 3)
- Stable dosing of Levodopa/Carbidopa prior to study
- ~18 patients (Part A); ~12 patients (Part B)
- Positive Part A could lead to Part B

Key Endpoints

- Safety, tolerability and pharmacokinetics
- Change from baseline in MDS-UPDRS Part III total score



SAGE-217

Well Positioned for Development in Broad Market CNS Indications

		Estimated U.S. Patient Population
Mood Disorders	Postpartum Depression:	• ~500,000 - 750,000 new diagnoses per year[1,2] • Up to 80% moderate-severe[3]
	Major Depressive Disorder:	• ~16 million adults reported at least one major depressive episode in the past year[4]
Movement Disorders	Essential Tremor:	• ~6 - 7 million total patients[5]
	Parkinson's Disease:	• ~700,000 total patients[6] • 60,000 new diagnoses per year[7]

1. Hamilton et al, *National Center for Health Statistics*, 2015; 2. O'Hara MW, McCabe JE, *Annual Review of Clinical Psych*., 2013; 3. PACT, *Lancet Psychiatry*, 2015; 4. Nat. Inst. of Mental Health website, 2014; 5. Louis ED, Ottman R, *Tremor Other Hyperkinet Mov*, 2014. 6. Willis et al, *Neuroepidemiology*, 2010; 7. Parkinson's Disease Foundation.

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Conclusion

Jeff Jonas, MD - CEO

Expected Milestones

Program	Compound	Indication	2H 2016	1H 2017	2H 2017
GABA	SAGE-547	Super-Refractory Status Epilepticus	✓ EMA Scientific Advice	○ Ph 3 top-line data	
		Postpartum Depression	✓ Ph 2 top-line data ✓ FDA BTD Meeting ✓ EMA PRIME ✓ Ph 3 initiation	○ EMA Scientific Advice	○ Ph 3 top-line data ▪ 202B - Severe ▪ 202C - Moderate
	SAGE-217	Postpartum Depression	○ Ph 2 initiation		○ Ph 2 top-line data
		Major Depressive Disorder	○ Ph 2 initiation	○ Ph 2 open-label data	
		Essential Tremor	✓ Ph 2 initiation		○ Ph 2 top-line data
		Parkinson's Disease	✓ Ph 2 initiation	○ Ph 2 open-label data	
	SAGE-105, SAGE-324	Orphan Epilepsies, GABA Hypofunction	○ Initiate IND-enabling studies		
NMDA	SAGE-718	Cerebrosterol Deficit Disorders	✓ Initiate IND-enabling studies	○ Ph 1 initiation	○ Ph 1 SAD data
		Anti-NMDA Receptor Encephalitis			
		NMDA Hypofunction			

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RETHINKING CNS

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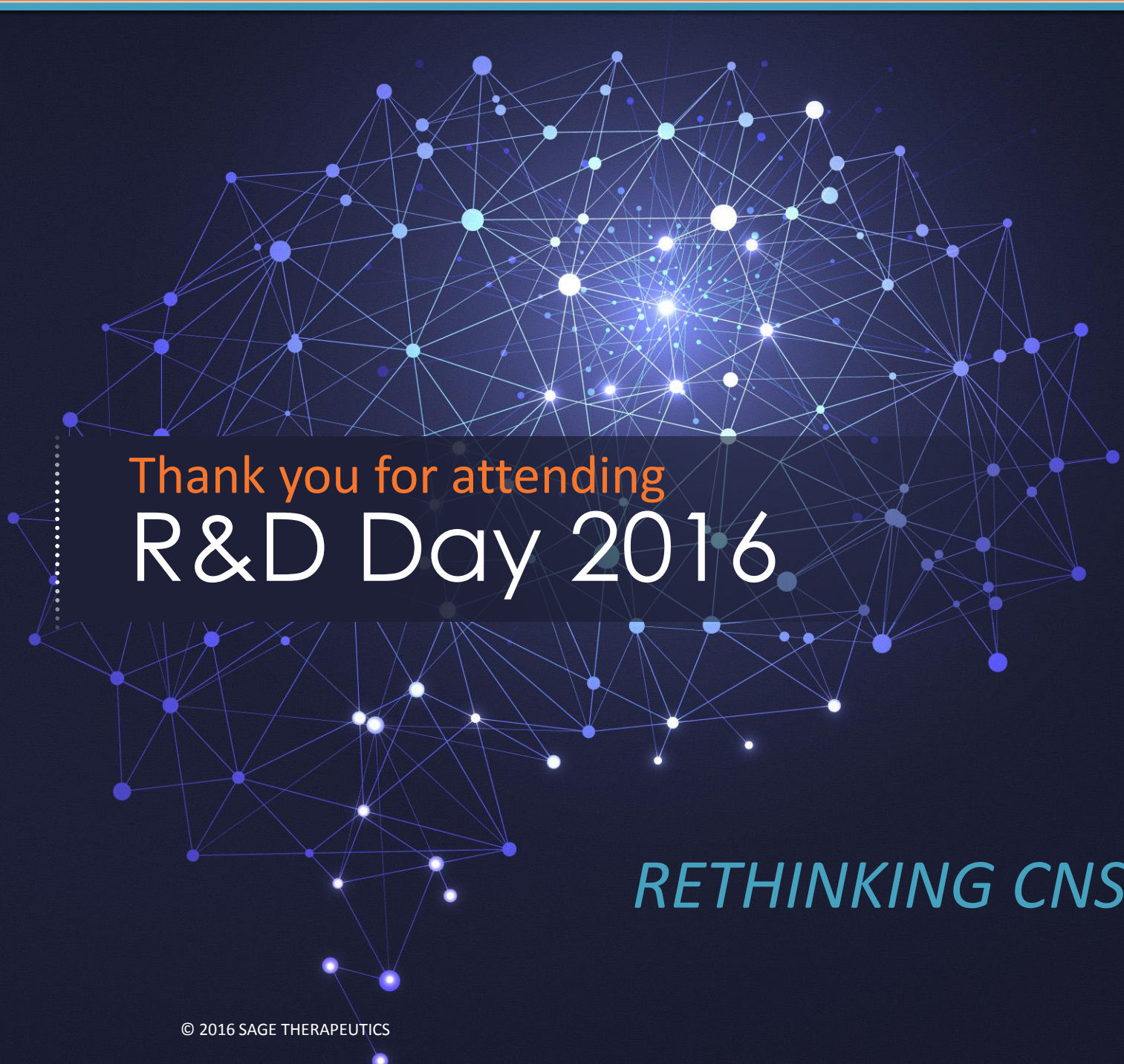
Q&A



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Thank you for attending

R&D Day 2016

RETHINKING CNS

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