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Sage *FutureCast*

An R&D and Portfolio Review

July 24, 2019

Safe Harbor Statement

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,” “can”, “could”, “chances”, “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: our expectations regarding: our planned activities, goals and strategy and potential timing and results; our belief in the potential of our product candidates and portfolio; the estimated number of patients with certain disorders or diseases or that may benefit from our drugs in the future; the potential for development of our products candidates in various indications; the potential profile, benefit and goals for our product candidates and their potential to change treatment paradigms and improve lives, if we are successful; and our views with respect to potential value creation opportunities and our ability to become a multi-franchise, leading CNS company. 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 our control, which could cause actual results to differ materially from those contemplated in these forward-looking statements, including the risk that:

- Success in pre-clinical studies or in earlier stage clinical trials of our product candidates may not be repeated or observed in ongoing or future studies involving the same compound or other product candidates, and future non-clinical and clinical results for our product candidates may result in a different product profile than we expect or not support further development of the product candidate or regulatory approval on the timelines we expect, or at all, or may require additional clinical trials or nonclinical studies;
- Even if our planned development programs are successful, we still may not achieve regulatory review or approval, despite prior regulatory advice, and regulatory authorities may ask for additional trials or data;
- We may experience slower than expected initiation or enrollment in our clinical trials or may encounter other delays or problems, including in analyzing data or requiring the need for additional analysis, data or patients, and such issues with any trial could cause delay in completion of the trial, availability of results and timing of future activities;
- Even if our 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 our current estimates; or we may not achieve market acceptance or reimbursement at acceptable levels;
- We may encounter unexpected safety or tolerability issues with respect to any of our product candidates or marketed products;
- We may not be able to obtain and maintain adequate intellectual property protection or other forms of data and marketing exclusivity for our products, or to defend our patent portfolio against challenges from third parties;
- We may face competition from others developing products for similar uses as those for which our products are being developed;
- Funding to support operations may not be available, when needed, on reasonable terms or at all, which may cause us to limit our development activities and change our plans;
- We may not be able to establish and maintain key business relationships with third parties on the terms we expect; and
- We may encounter technical and other unexpected hurdles in the manufacture and development of our products.

For additional disclosure regarding these and other risks Sage faces, see the disclosure contained in the "Risk Factors" section of our most recent quarterly report, and in our 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 our views only as of today, and should not be relied upon as representing our views as of any subsequent date. We undertake 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.

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Presenters

Jeff Jonas
M.D., Chief Executive Officer

Jim Doherty
Ph.D, Chief Research Officer

Rob Lasser
M.D., Vice President, Late Development

Helen Colquhoun
M.D., Vice President, Early Development

Aaron Koenig
M.D., Medical Director, Early Development

Agenda

Introduction

R&D Strategy: Sage's Differentiated Approach to Drug Development

SAGE-217: Expanding opportunities for impact in mental health

SAGE-324: Novel potential treatment for chronic neurological conditions

SAGE-718: Novel positive allosteric modulator of NMDA receptors for treatment of cognitive dysfunction

Conclusion

Q&A
Presenters + Kimi Iguchi, Chief Financial Officer, available for Q&A

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Seeing the brain differently *makes a world of difference*

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Sage's Differentiated Approach to Drug Development

Improving the probability of success

Jim Doherty, Ph.D.
Chief Research Officer

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Rethinking Neuroscience
Bridging translational science & experimental medicine

Translational Neuroscience

- Identify functional biomarkers in animals
- Establish genetic and biochemical criteria to select patient populations
- Translate insights between compounds and indications for better odds of success across pipeline

Experimental Medicine

- Conduct human studies
- Leverage opportunities to inform development strategy for Sage programs and compounds
- Deliver new biomarkers (physiological / biochemical / genetic)

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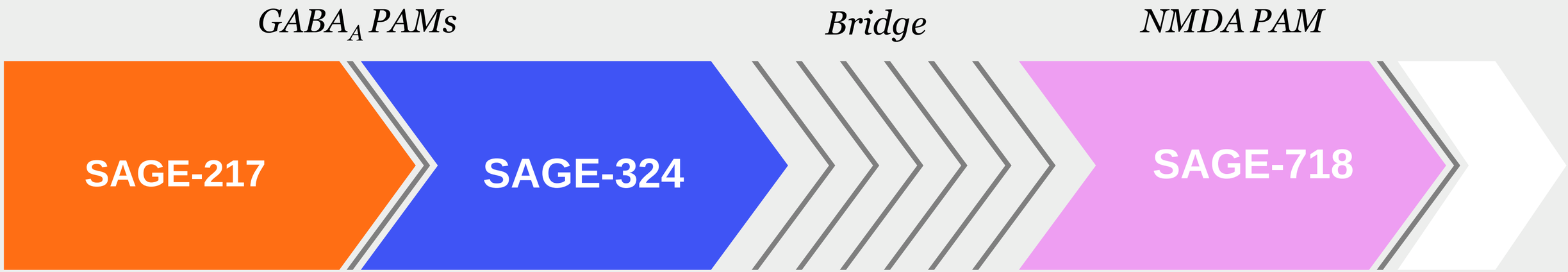
Rethinking Neuroscience
Sage's distinct integrated approach



- By following the science and designing efficient trials, Sage pursues serial de-risking
  - Data from completed studies on dosing, tolerability, biomarkers inform design of new trials
  - Studies are designed to bridge the gap from targets in context to therapeutic utility
- De-risking strategy can be used for either the same molecule or a related molecule from the Sage pipeline
  - Target small, focused indication studies with opportunities to expand into larger therapeutic indications

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SAGE-217
Expanding opportunities for impact in mental health

Robert Lasser, M.D.
Vice President, Late Development

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SAGE-217
Encouraging signals in three additional distinct indications

Major Depressive Disorder (MDD)
17M
MOUNTAIN, SHORELINE & MDD-302 Studies
Insomnia in MDD (RAINFOREST Study)

Treatment Resistant Depression (TRD)
3M
MDD-201B & ROBIN Studies

Pediatrics
2M
Planned Global Study

Suicide attempts
1.4M

Geriatrics
1M
SHORELINE Study

Postpartum Depression (PPD)
0.4M
ROBIN Study

Generalized Anxiety Disorder (GAD)
7M
*MDD-201B & ROBIN Studies**

Bipolar Depression (BPD)
3M
*ARCHWAY Study**

*Source: Sage epidemiology estimates, approximate values; *Subpopulation extrapolation*

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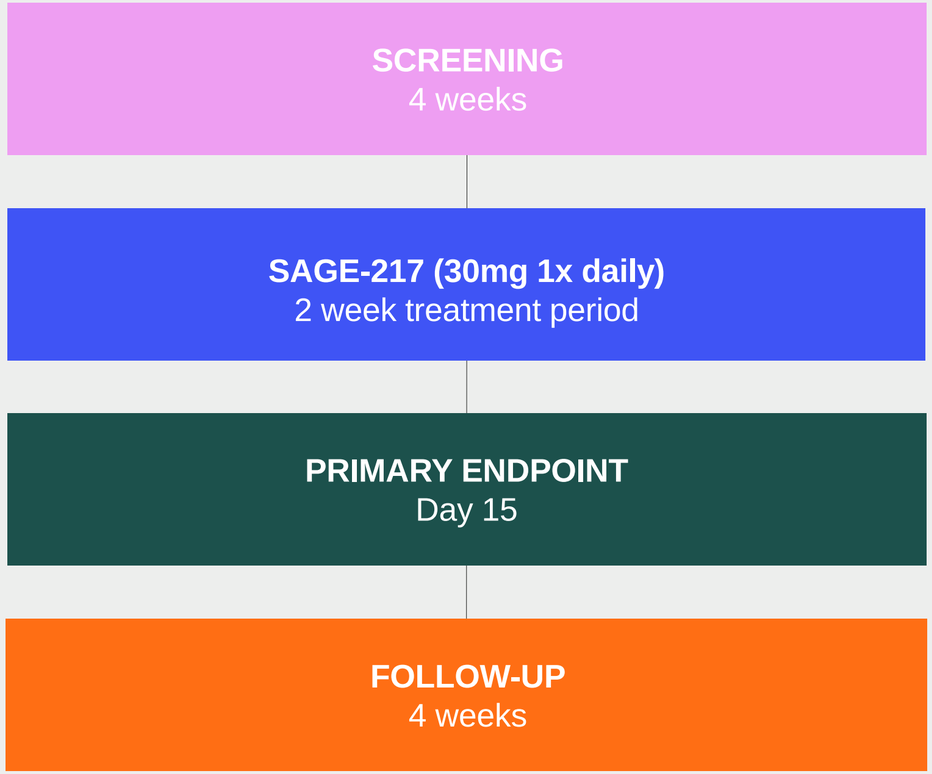
SAGE-217 ARCHWAY Study in Bipolar Depression (BPD)
Phase 2 open-label, signal-finding study

- Bipolar disorder (including Types I and II) directly affects about 3 to 6 million adults in the U.S., with an age of onset in late-teens to 20s
- BPD may have a distinct biology, presenting differently compared to unipolar MDD, and may respond differently versus MDD to medications
  - Polypharmacy, notably mood stabilizers and atypical antipsychotics are standard of care
- Given risk of switch to mania with antidepressants, an episodic approach with a novel MOA might mitigate manic switching
- Sage has completed an open-label study of SAGE-217 in bipolar depression, using the same dosing approach as with unipolar depression



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SAGE-217 ARCHWAY Study in BPD
Population, Safety

- Open-label trial of SAGE-217 taken 30mg each evening for 14 days
- n=35**:** 89% bipolar disorder Type I; mean age of 47.6; 66% female
  - 40% taking anti-depressants and/or mood stabilizers at baseline
  - Employment, marriage and educational characteristics suggest a sample with low functional status, consistent with population profile
- Discontinuation rate of 29%, similar to other recent trials in bipolar depression; no discontinuations from adverse events

Adverse events	SAGE-217 (%)
Somnolence	4 (11.4)
Headache	3 (8.6)
Diarrhea	2 (5.7)
Sedation	2 (5.7)
Hypomania	2 (5.7)

- AEs reported in 46%; 66% mild, no severe or serious events
- No dose reductions, loss of consciousness or syncope, no signal for increased suicidal ideation or behavior compared to baseline (as measured by C-SSRS), no clinically significant changes in vital signs or clinical laboratory parameters or ECGs
- No mania; 2 cases of transient hypomania off-treatment

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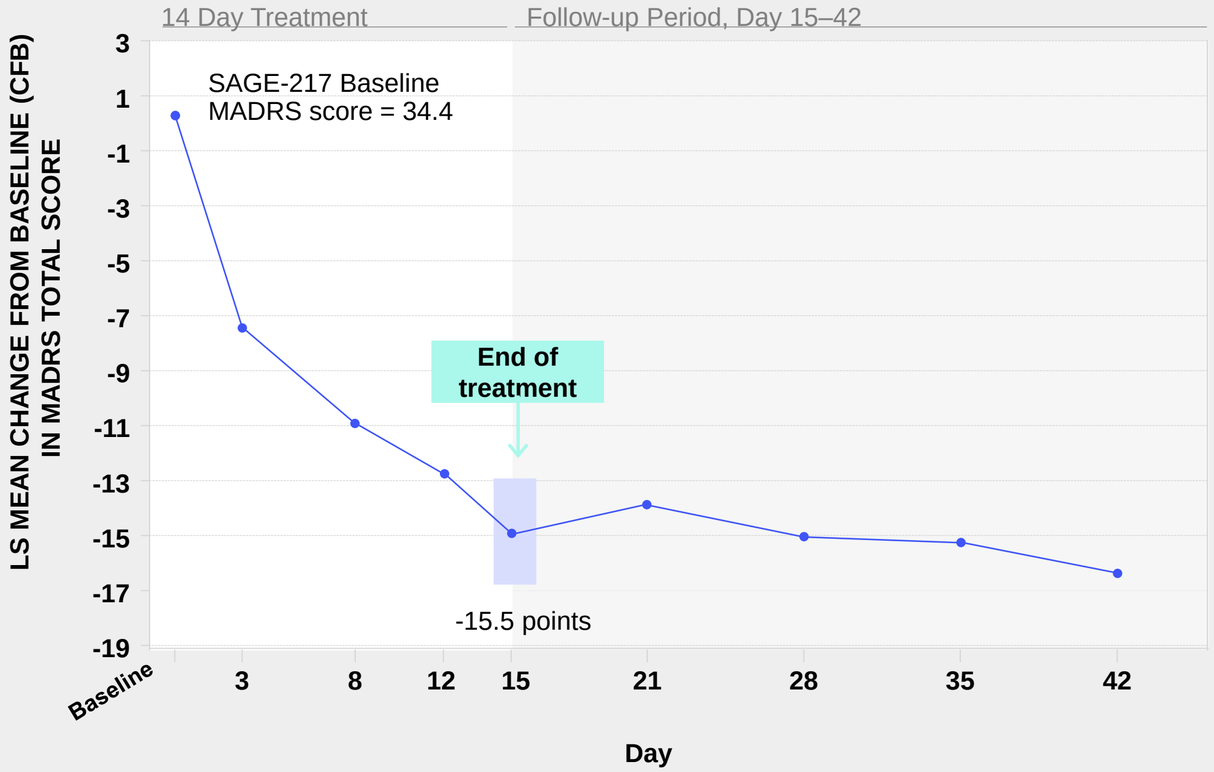
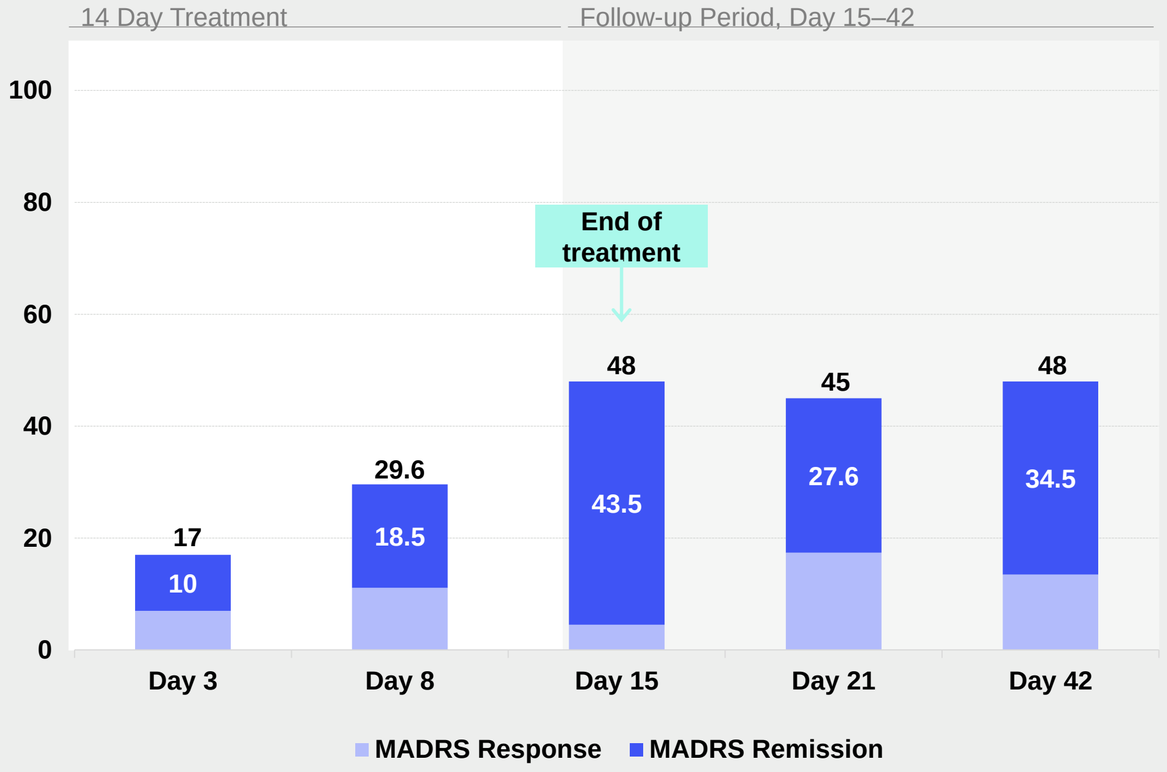
SAGE-217 ARCHWAY Study in BPD
Improvement in depression symptoms (MADRS)



% RESPONSE (≥ 50% IMPROVEMENT IN MADRS TOTAL SCORE) AND REMISSION (MADRS ≤ 12)



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Treatment-resistant depression (TRD)
Post hoc analysis of anti-depressant unresponsive subjects in Phase 3 SAGE-217 program

Significant opportunity for innovation in TRD treatments

TRD accounts for ~15% to 20% MDD samples and is associated with greater costs and disability than responsive depression[1]

- TRD indication could provide strong support for first-line use of SAGE-217 across all MDD, assuming strong signal, efficient development pathway
- May also provide data-driven approach to certain cost-focused markets
- For analysis, trial participants in pivotal SAGE-217 MDD and PPD studies who were unresponsive to either average or high-dose anti-depressants at baseline were examined to assess signal for SAGE-217 potential utility in TRD

[1]*Amos TB, et al. J Clin Psych 2018; 79(2)*

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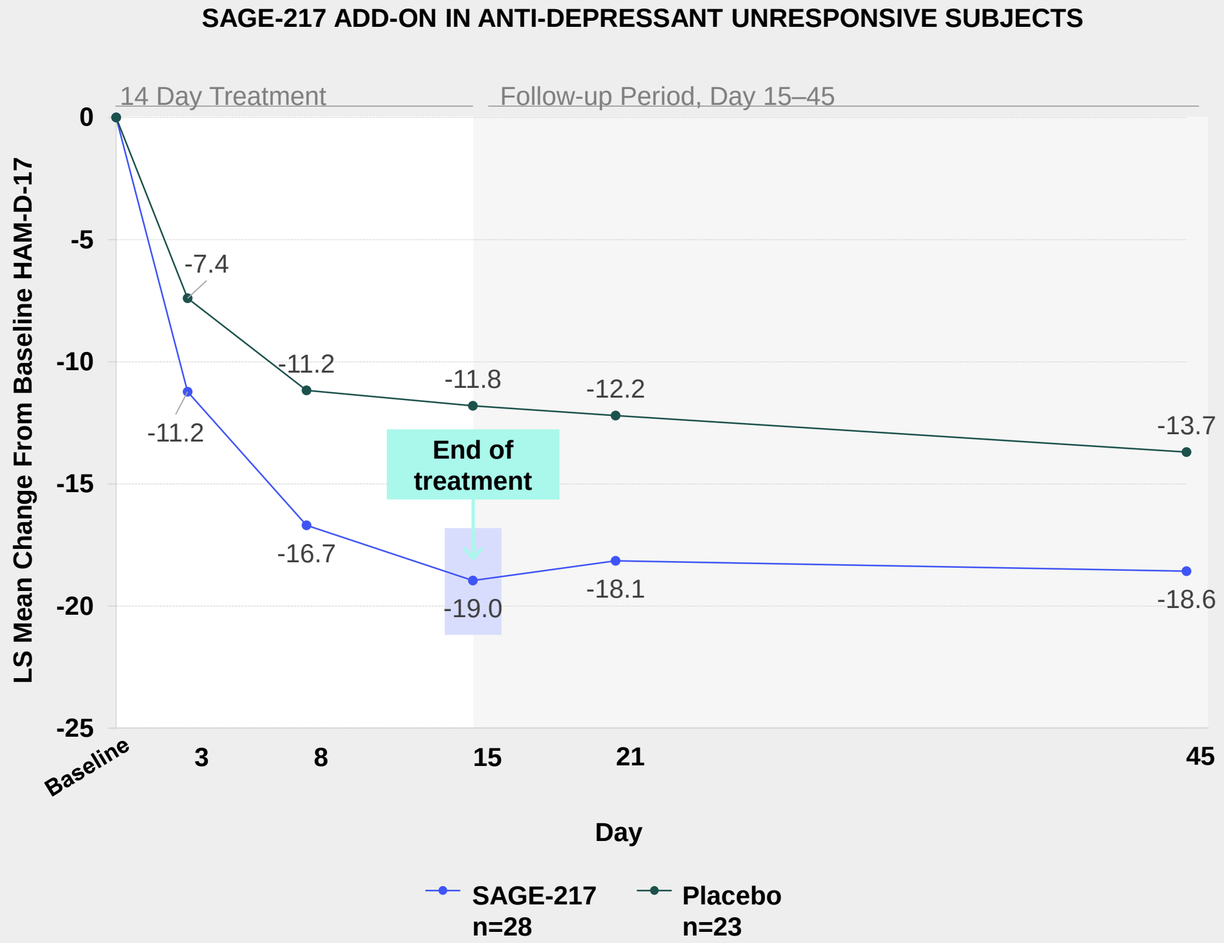
SAGE-217
Treatment response in people unresponsive to standard of care

- Sage conducted a post hoc analysis of 51 patients from the MDD-201B and ROBIN Studies with ongoing symptoms of depression despite receiving standard anti-depressant pharmacotherapy
  - 25% of subjects from MDD-201B and ROBIN Studies met criteria
- Treatment response is similar in subjects on anti-depressants who had a major depressive episode despite being on these medications



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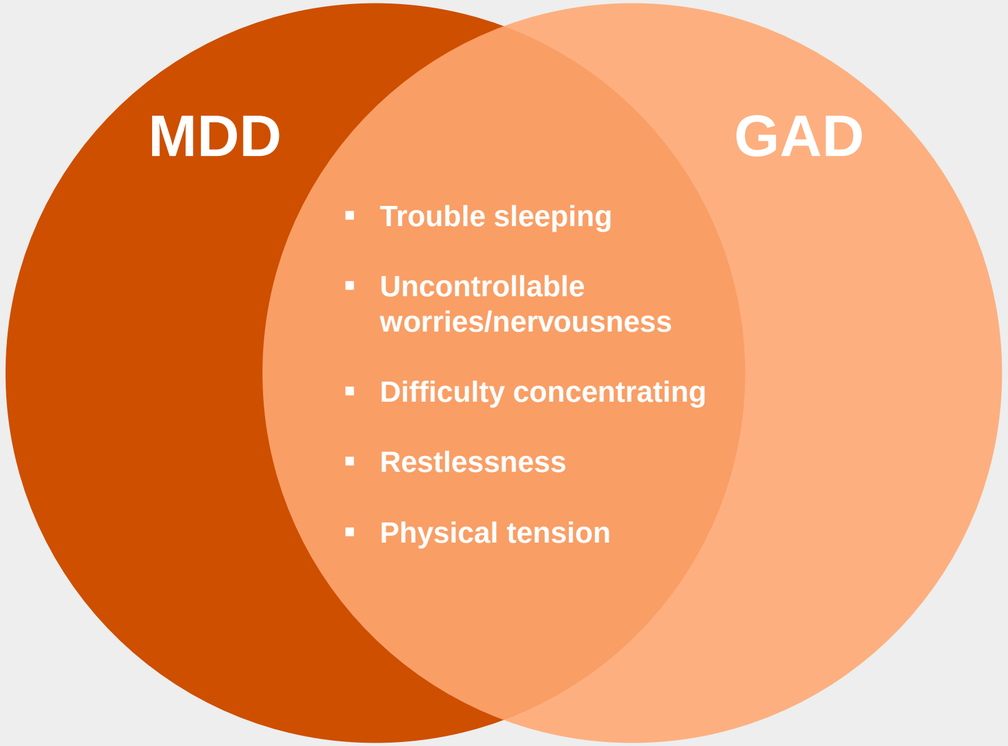
Generalized Anxiety Disorder (GAD)
Adjacent area of depression with unmet need

Substantial symptom overlap of GAD with MDD



- An estimated 6 million individuals suffer from GAD in the US
- Standard treatment is with anti-depressants
- Significant benefit in co-morbid anxiety symptoms in depression suggests that similar, durable improvements in anxiety associated with GAD may be possible
- GAD as a “chronic” illness may be amenable to “episodic” reframing
- Substantial clinical and societal value for a therapy to replace chronic benzodiazepine use

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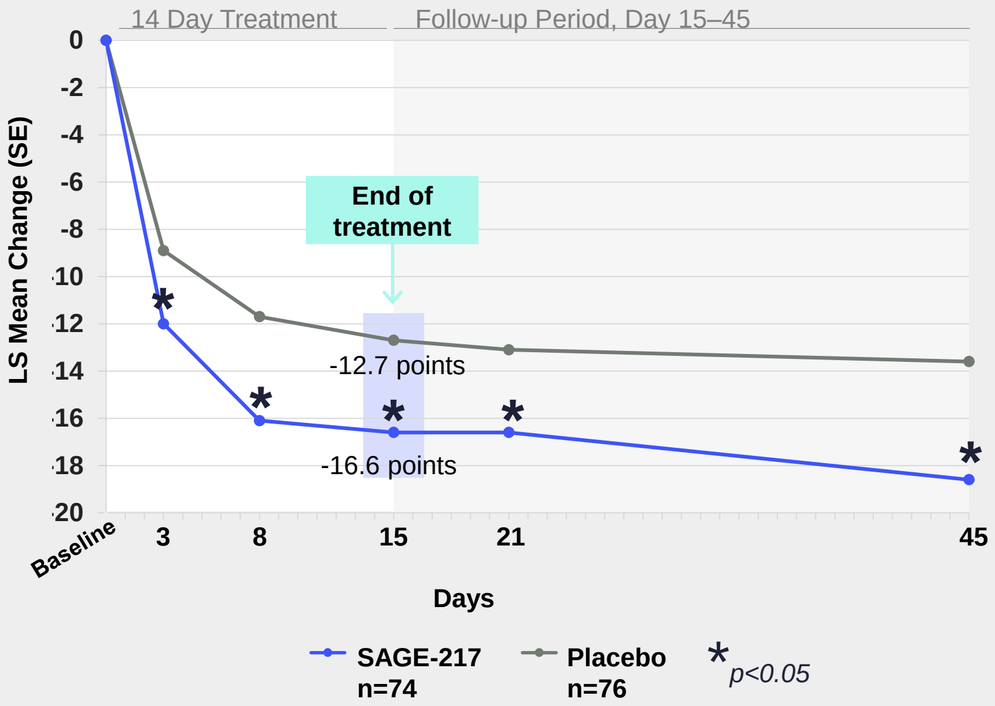
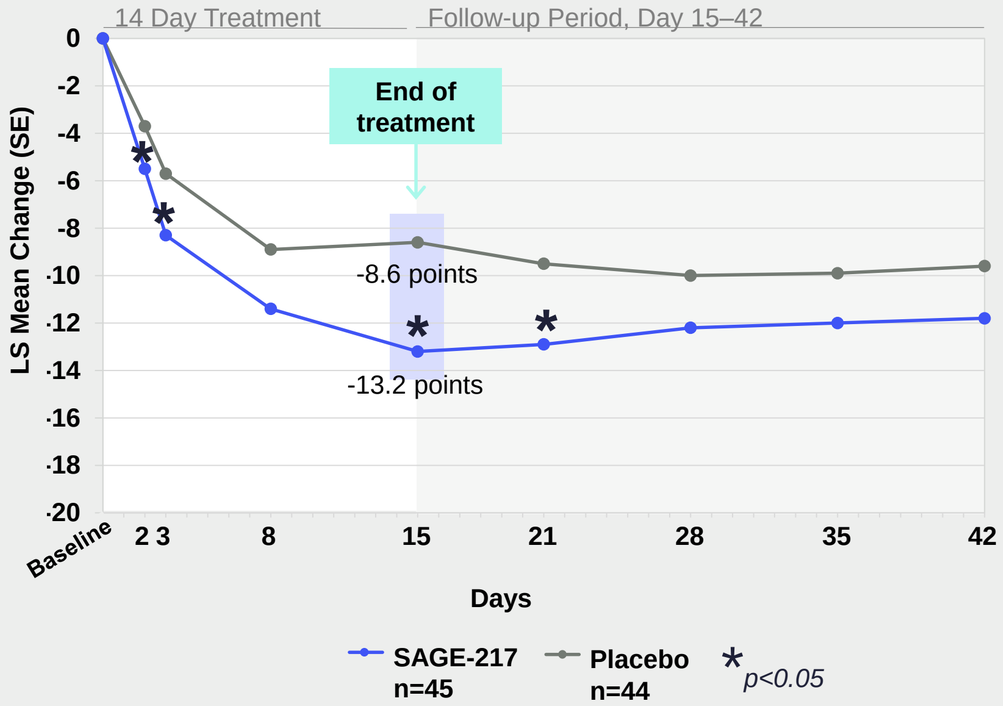
Generalized Anxiety Disorder
Robust impact on anxiety symptoms

DEPRESSION

HAM-A SCORE: ROBIN STUDY



HAM-A SCORE: 217-MDD-201B



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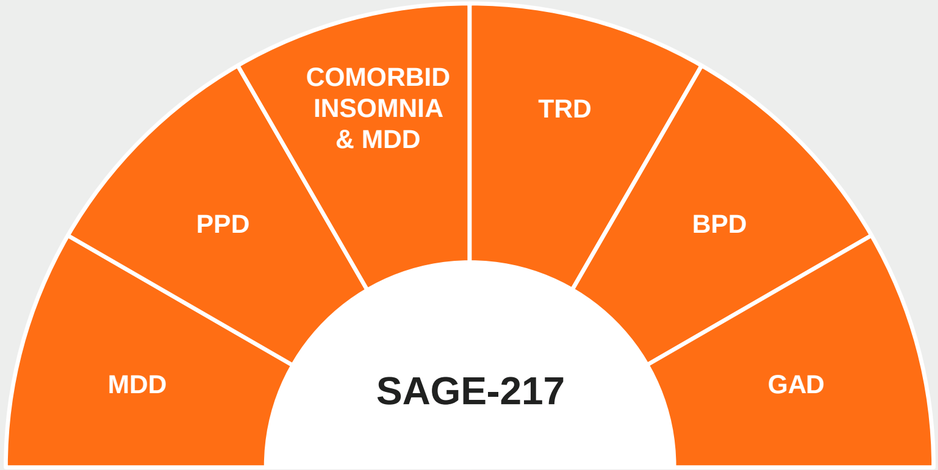
SAGE-217
Planned program expansion to TRD

- Emerging SAGE-217 evidence suggests multiple areas of expansion possible
  - Data in bipolar depression indicate potential benefit, prudent to conduct a blinded trial when best aligned with value creation
  - Data from individuals with at least one anti-depressant failure at baseline (TRD proxy; ad hoc) suggest strong response
  - Data reflecting the anti-anxiety effect are compelling, may require pilots to examine durability in GAD
- MDD-301 (MOUNTAIN study) continues on-track with expected read-out 4Q19/1Q20
- Decision to move into TRD as the next expansion of the Landscape Program
  - Potentially requires fewer development resources; offers another potential near-term value creation opportunity; and remains of high interest to the clinical community



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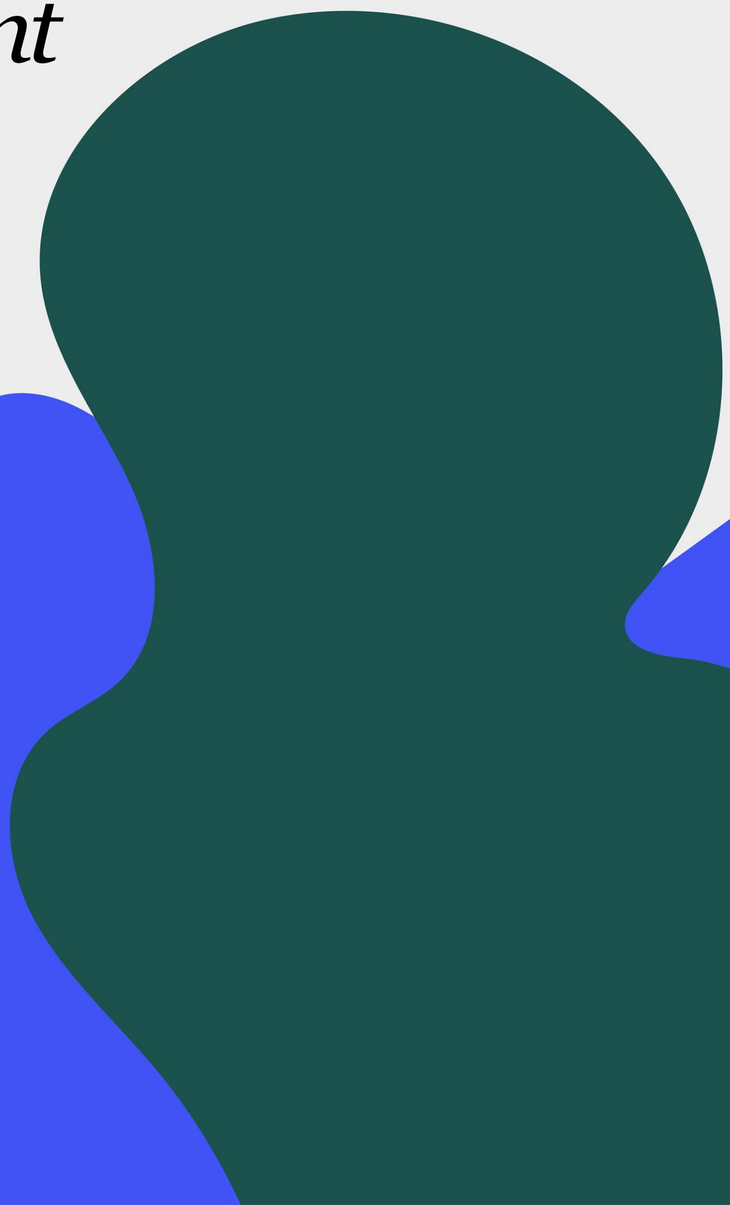
SAGE-324
Novel potential treatment for chronic neurological conditions

Helen Colquhoun, M.D.
Vice President, Early Development



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Essential Tremor
Common movement disorder where SOC may be inadequate for many

NEUROLOGY

Disease Overview

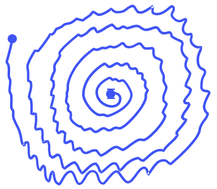
- Most prevalent movement disorder, estimated to affect more than 6M people in the U.S.; 1M seek treatment
- High unmet need; 50% of treated patients do not respond or have sub-optimal response to standard of care (SOC)[1]

Pathophysiology

- Associated with reduction in GABAergic tone in cerebellum and thalamus[2]
  - Reduced GABA levels and diminished receptor volume have been found in CSF and in postmortem analyses[3]

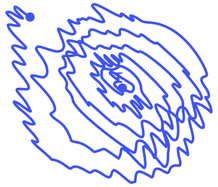
Mild

Difficulty with fine motor tasks that require precision



Moderate

Difficulty with everyday tasks



Severe

Significant impairment in activities of daily living and independence

Decreasing ability to:

Work
Do chores/yardwork
Use a phone
Write
Cook
Use transportation
Walk
Take medication
Get dressed
Self-care
Drink
Eat

Source: [1]Louis et al., Eur J Neurol 2010 [2]Paris-Robidas S et al., Brain 2011 [3]Mally et al., J Neural Transm 1996

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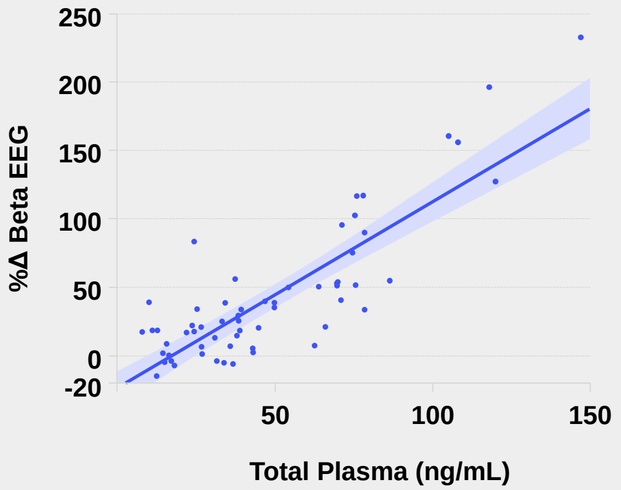
SAGE GABA PAMs
Predictable pharmacodynamic effects and activity in Essential Tremor

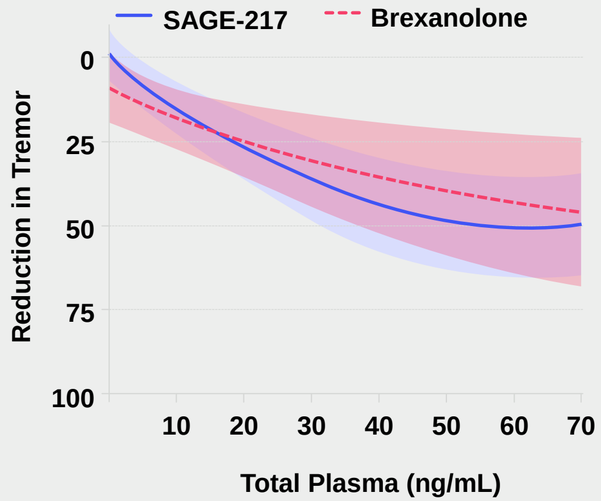
NEUROLOGY

	BREXANOLONE	SAGE-217
Drug Exposure	✓	✓
Target Engagement (Change in β-EEG)	✓	✓
Activity in Essential Tremor	✓	✓

SAGE-217 TARGET ENGAGEMENT



SAGE GABA PAMs REDUCE TREMOR



- After a single dose, both brexanolone and SAGE-217 demonstrated reduction in tremor in ET patients
- Profile mirrored drug exposure and degree of target engagement as measured by change from baseline β-EEG

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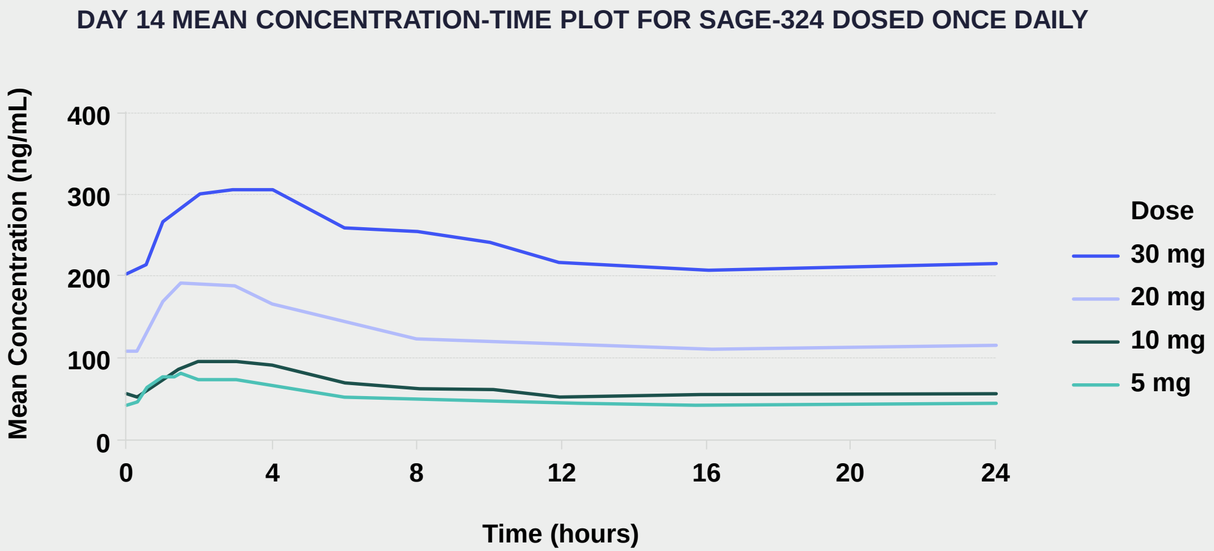
SAGE-324
Pharmacokinetics are well-suited to Essential Tremor

NEUROLOGY

SAGE-324
Drug Exposure ✓
Target Engagement (Change in β-EEG)
Activity in Essential Tremor



- Good oral bioavailability
- Long half-life (90-120 hours)
- Profile provides flexibility in dosing paradigms

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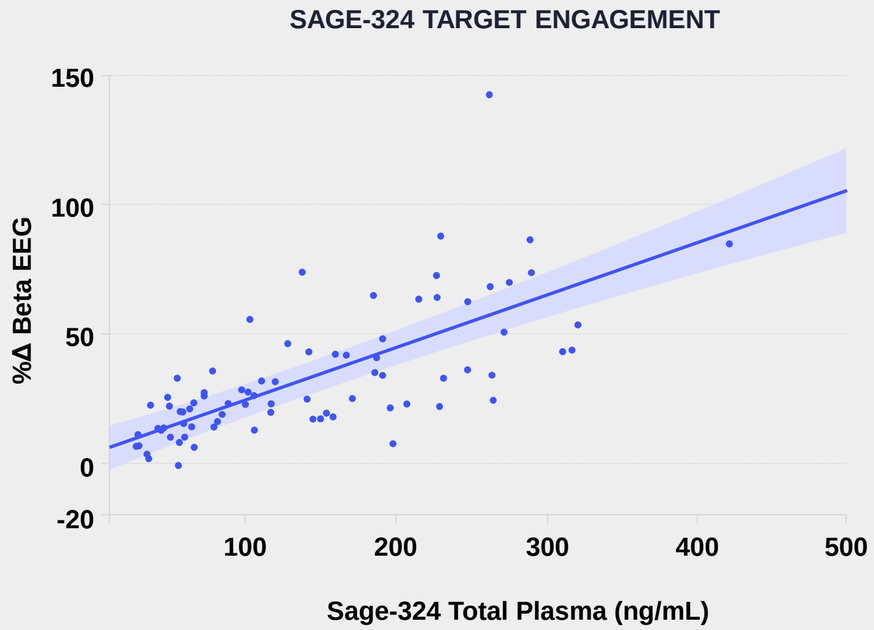
SAGE-324
Target engagement demonstrated with β-EEG biomarker

NEUROLOGY

	SAGE-324
Drug Exposure	✓
Target Engagement (Change in β-EEG)	✓
Activity in Essential Tremor	



- Brexanolone and SAGE-217 clinical data established bridge between drug exposure, EEG, and tremor reducing activity
- Same methodology was applied to SAGE-324 β-EEG data, demonstrated target engagement at doses significantly lower than maximum tolerated dose

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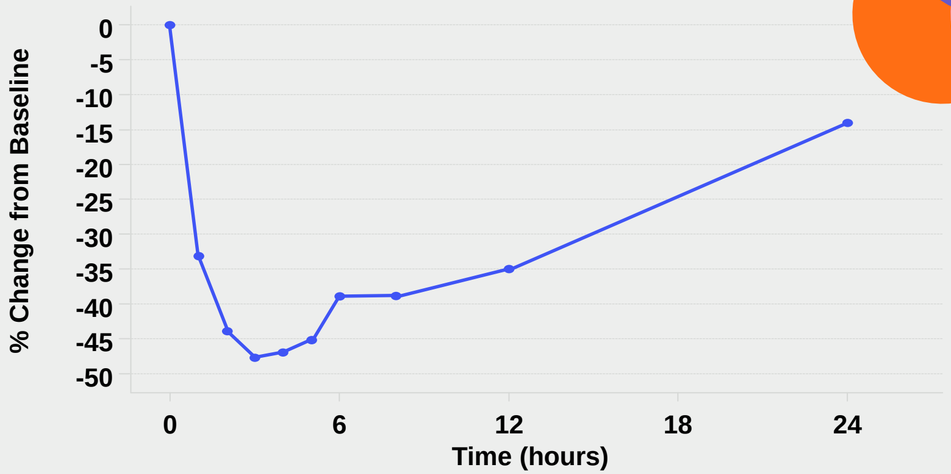
SAGE-324
Tremor reduction in ET patients observed after a single dose

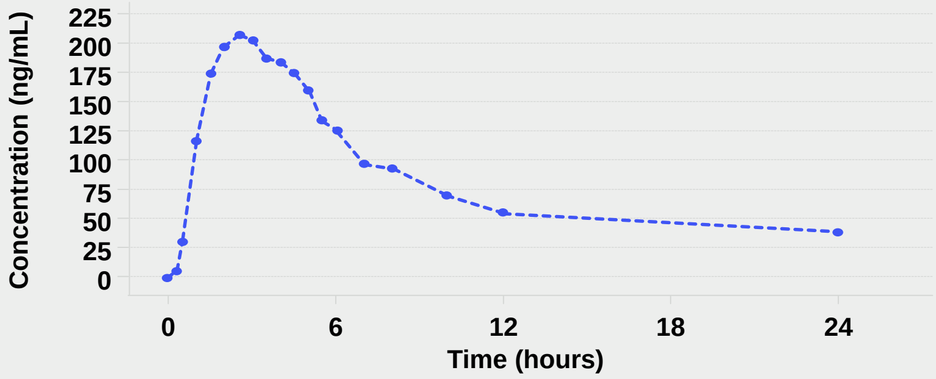
NEUROLOGY

SAGE-324
Drug Exposure ✓
Target Engagement (Change in β-EEG) ✓
Activity in Essential Tremor ✓

Total upper limb combined score change after SAGE-324 dosing in 6 people with ET as measured by accelerometer



PK over time in 6 people with ET dosed with SAGE-324



- Clear PK/PD relationship
- Promising signals of tremor reduction, consistent with those observed previously for brexanolone and SAGE-217
- SAGE-324 was well-tolerated in ET patients

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SAGE-324
Well-positioned for development in ET and other chronic neurologic conditions

	SAGE-324
Drug Exposure	✓
Target Engagement (Change in β-EEG)	✓
Activity in Essential Tremor	✓

- PK/PD relationships for brexanolone and SAGE-217 in Essential Tremor reproduced with SAGE-324
- Pharmacodynamic markers (β-EEG) will support dose ranging in Phase 2 to explore efficacy and tolerability of SAGE-324 in Essential Tremor
- SAGE-324's long half-life will provide consistent plasma concentrations with minimal daily fluctuations after multiple doses
- SAGE-324 was well-tolerated in Phase 1 studies; most common adverse events were somnolence, dizziness, and feeling of relaxation

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SAGE-718
Novel NMDA receptor PAM for potential treatment of cognitive dysfunction

Aaron Koenig, M.D.
Medical Director, Medical Science

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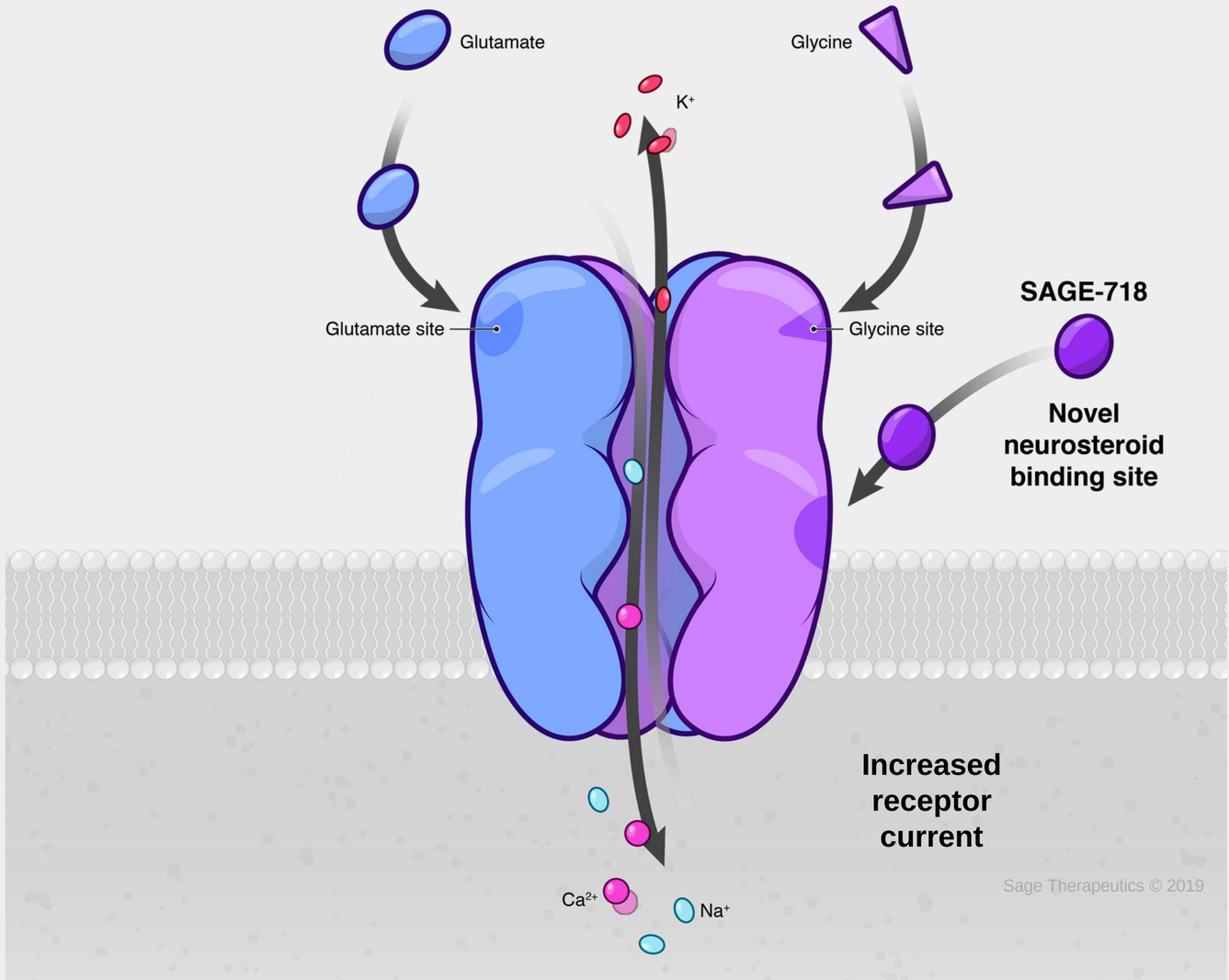
Sage's First-in-Class NMDA *Positive Allosteric Modulators*

- NMDA receptors are ionotropic glutamate receptors that play a key role in a host of cognitive and behavioral processes
- Sage identified an endogenous modulator of the NMDAR (24S-hydroxycholesterol) and initiated a research effort to discover novel NMDAR modulators
- Sage has built a library of novel oxysterol-based NMDA modulators, with unique profiles, that are in various stages of development, the first of these being SAGE-718

Endogenous & Exogenous Ligands at the NMDA Receptor



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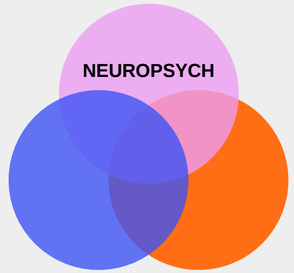
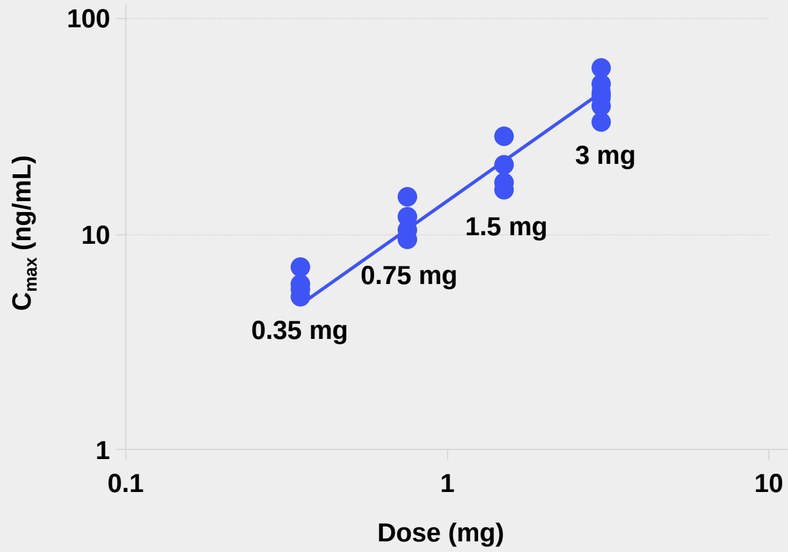
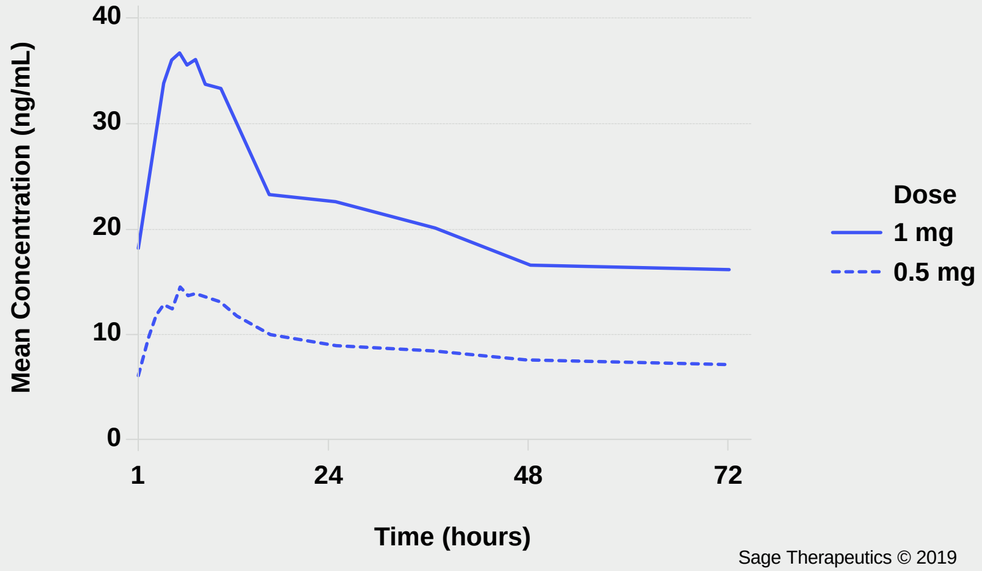
SAGE-718
Clinical profile supports development



- Five Phase 1 clinical studies (100+ subjects dosed) completed
- SAGE-718's pharmacokinetic profile supports once-a-day oral dosing
  - Plasma C_{max} and AUC exposure is dose-proportional
  - Long half-life is consistent with once daily dosing
- To date, SAGE-718 has an acceptable safety and tolerability profile
  - No serious adverse events or deaths
  - Most treatment-emergent adverse events were mild in severity
    - No treatment-emergent adverse events resulted in study drug discontinuation or dose reduction
    - No significant changes in clinical chemistry, hematology, urinalysis, or ECGs were observed





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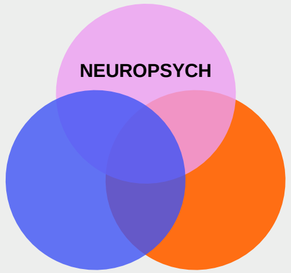
SAGE-718
Data suggest potentially transformational activity in the brain



- A suite of three experimental medicine studies was designed to investigate CNS-target engagement using a low-dose ketamine challenge paradigm

- Results from an integrated data analysis from all three studies demonstrate that SAGE-718:
  - Had effects on electrophysiological, functional imaging and cognitive endpoints in healthy volunteers consistent with CNS activity
  - Modulated the effects of ketamine on regional and global measures of resting brain activity indicating functional interaction with NMDA receptors

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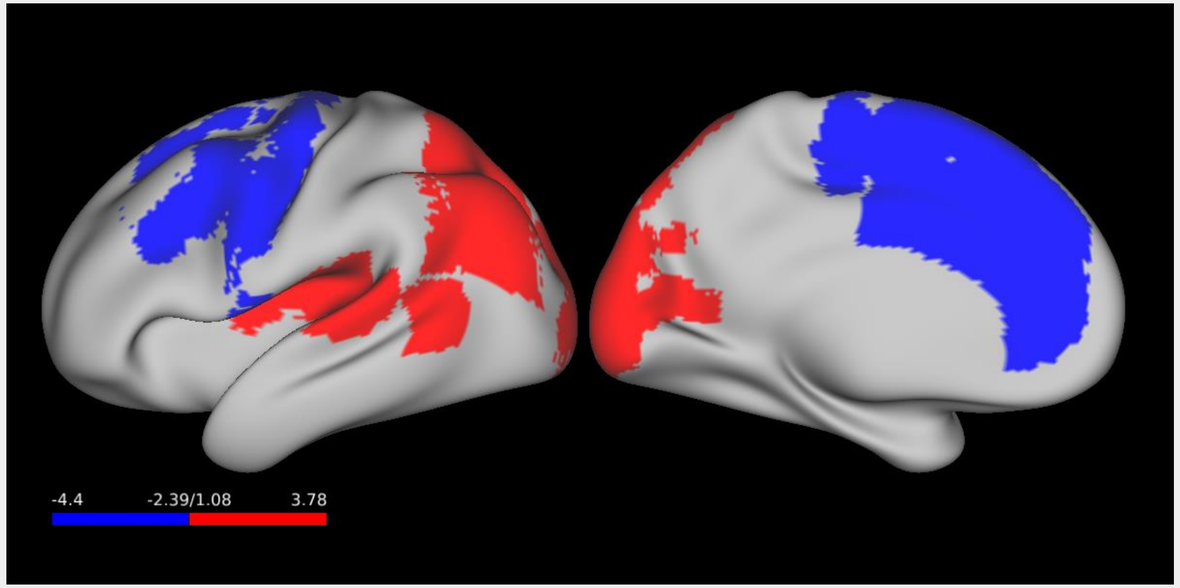
SAGE-718
Attenuated effects of ketamine on brain circuits, in Phase 1 study

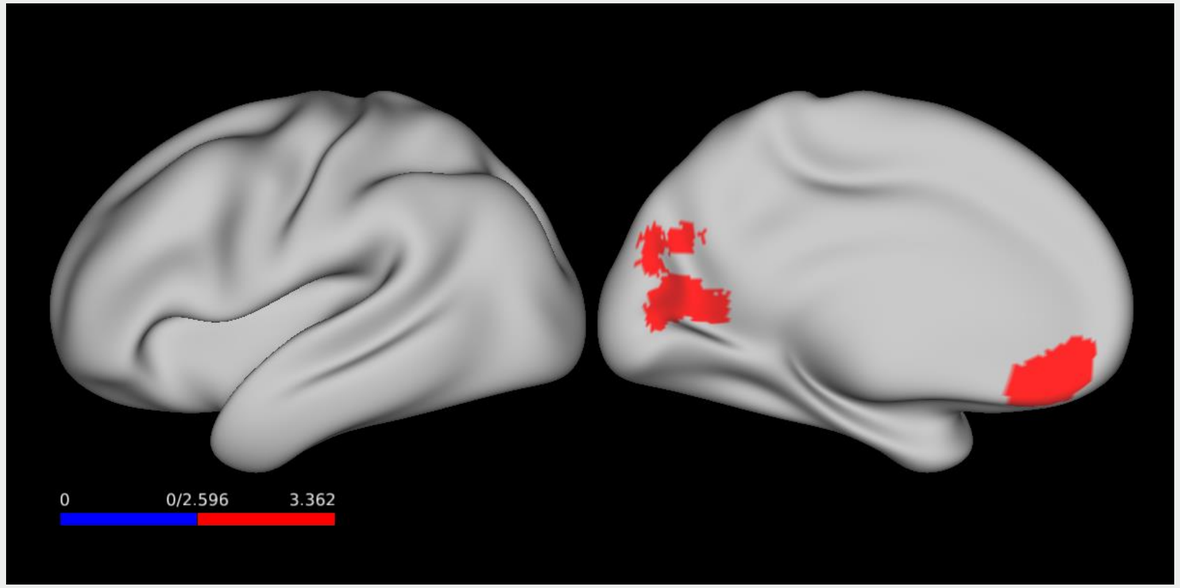
NEUROPSYCH

KETAMINE



Ketamine caused regionally localized increases (**RED**) and decreases (**BLUE**) in cerebral blood flow (BOLD-MRI)

SAGE-718 + KETAMINE



SAGE-718 blunted ketamine's induced increases and decreases in BOLD-MRI

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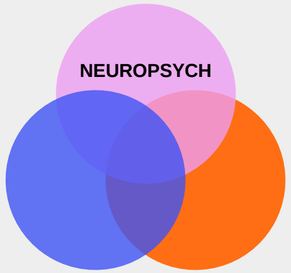
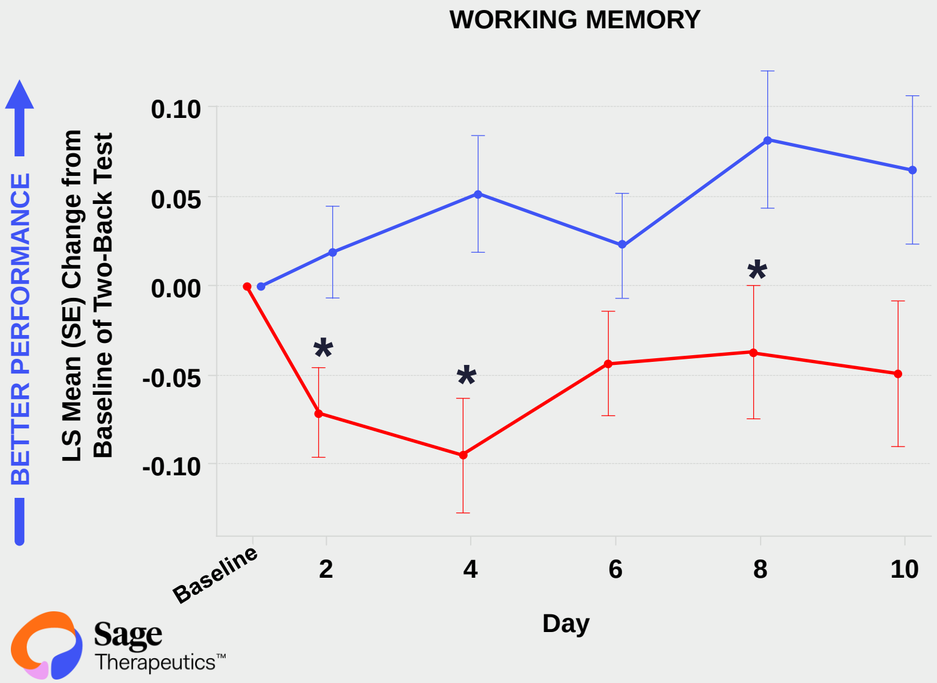
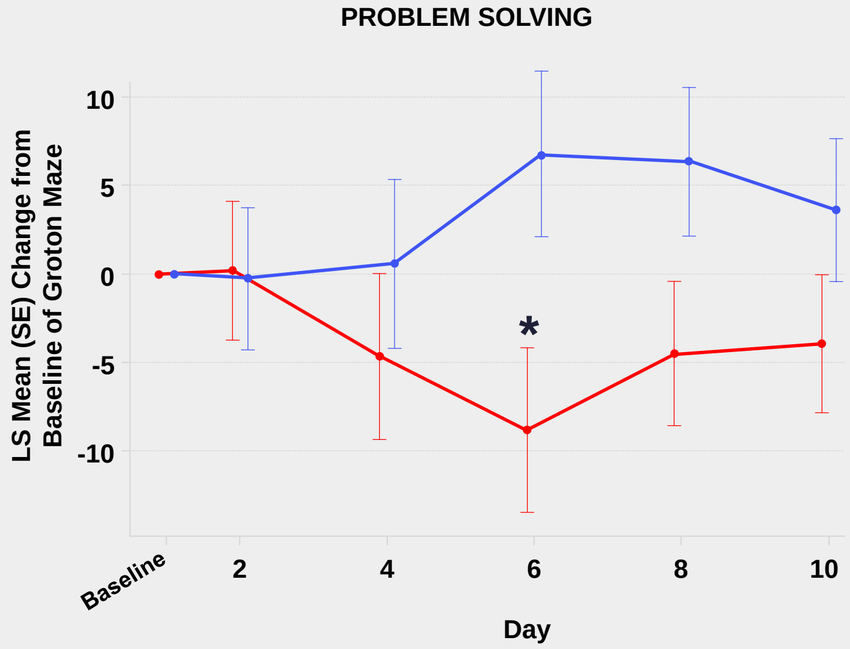
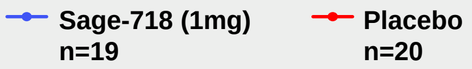


SAGE-718
Significantly improved executive functioning, in Phase 1 study

- Healthy volunteers dosed with SAGE-718 exhibited superior performance on tests of working memory and complex problem solving
- SAGE-718's profile is potentially distinct from that of other cognitive-enhancing compounds
  - SAGE-718's effects on cognition were not directly attributable to changes in reaction time or attention
  - SAGE-718 did not cause an increase in heart rate, blood pressure, cortisol release or psychiatric AEs







***p<0.05**. A MMRM model was applied with change from baseline in each cognitive assessment test score as the response variable and treatment, visit, visit-by-treatment interaction as fixed effect, baseline as covariate, and measurements within the same subject as repeated measure. Unstructured covariance structure was applied for the repeated measure.

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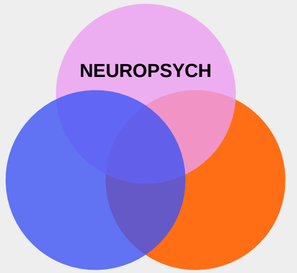
SAGE-718
May provide unique cognitive benefits across therapeutic indications



Findings in normal suggest a potential application for cognition beyond illnesses with NMDA hypofunction; executive function is a key component of brain health across life-span

NEURODEVELOPMENT

- Autism spectrum disorders
- Schizophrenia
- ADHD

COGNITIVE RECOVERY & REHABILITATION

- Post-encephalitic

NEURODEGENERATIVE DISEASES

- Alzheimer’s
- Parkinson’s
- Huntington’s

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Conclusion

Jeff Jonas, M.D.

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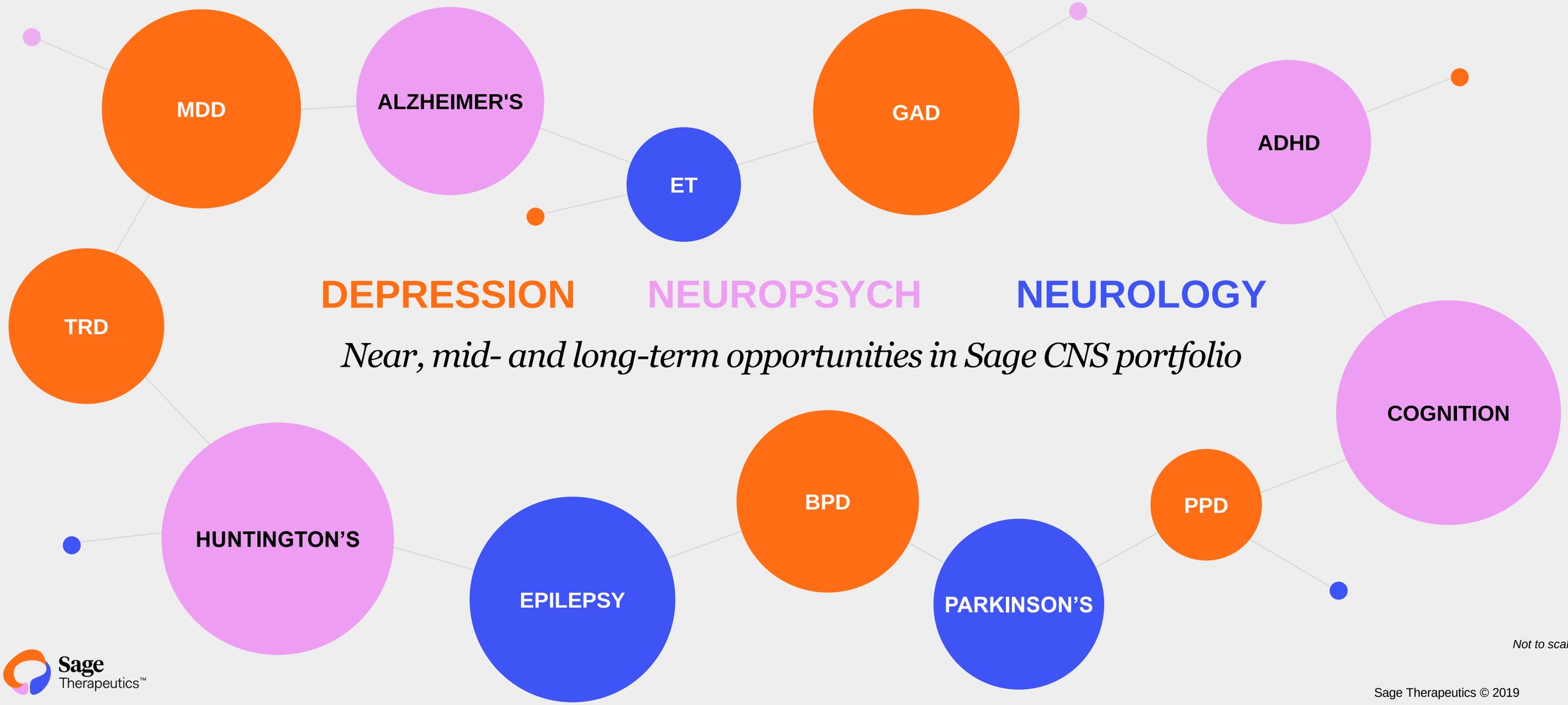
Translational work between adjacent indications *enables potential for rapid pipeline expansion…*



Not to scale

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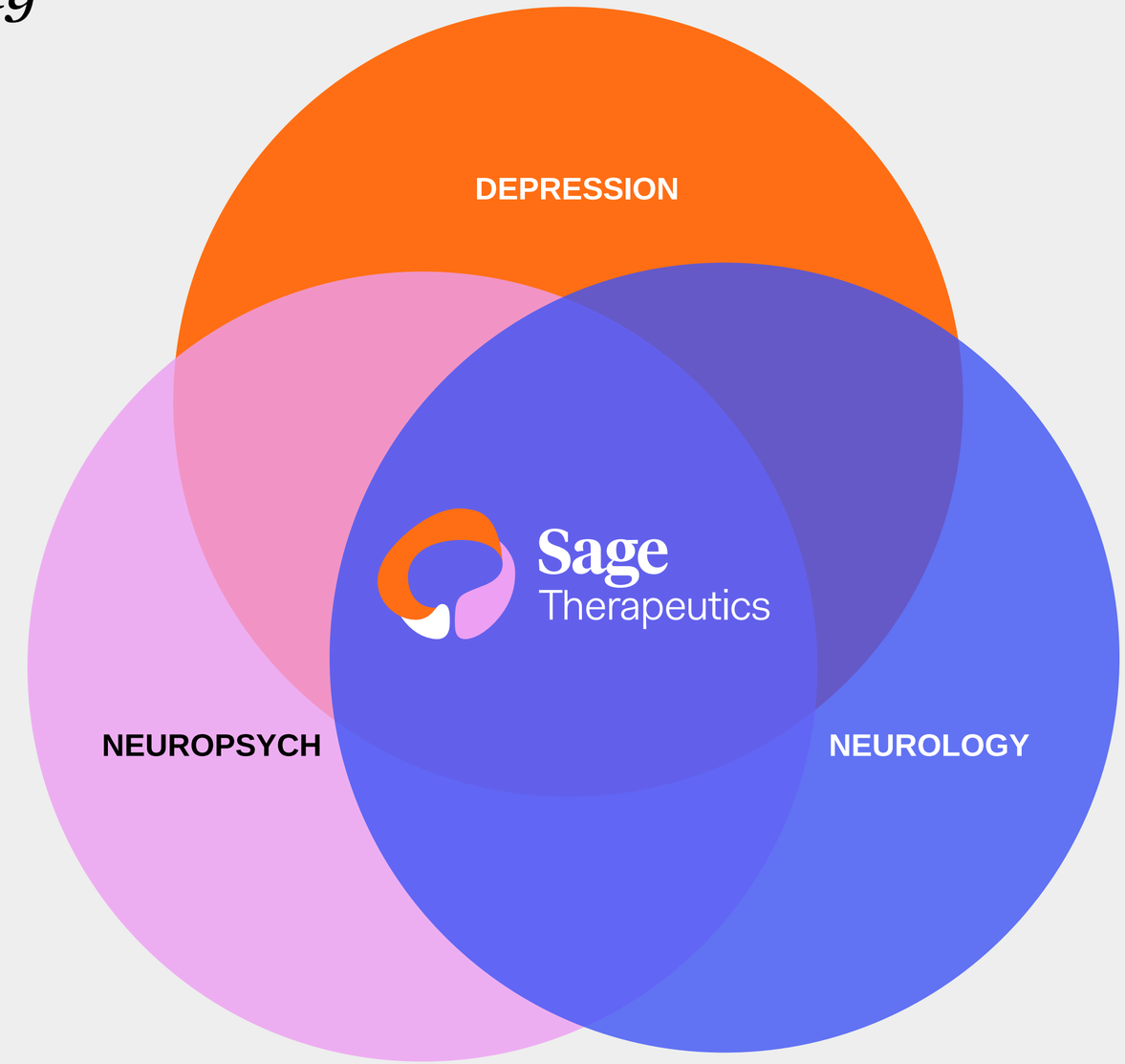
… to establish a multi-franchise *brain health company*



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Q&A

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