Sage Therapeutics™

# Investor Presentation

November 2020

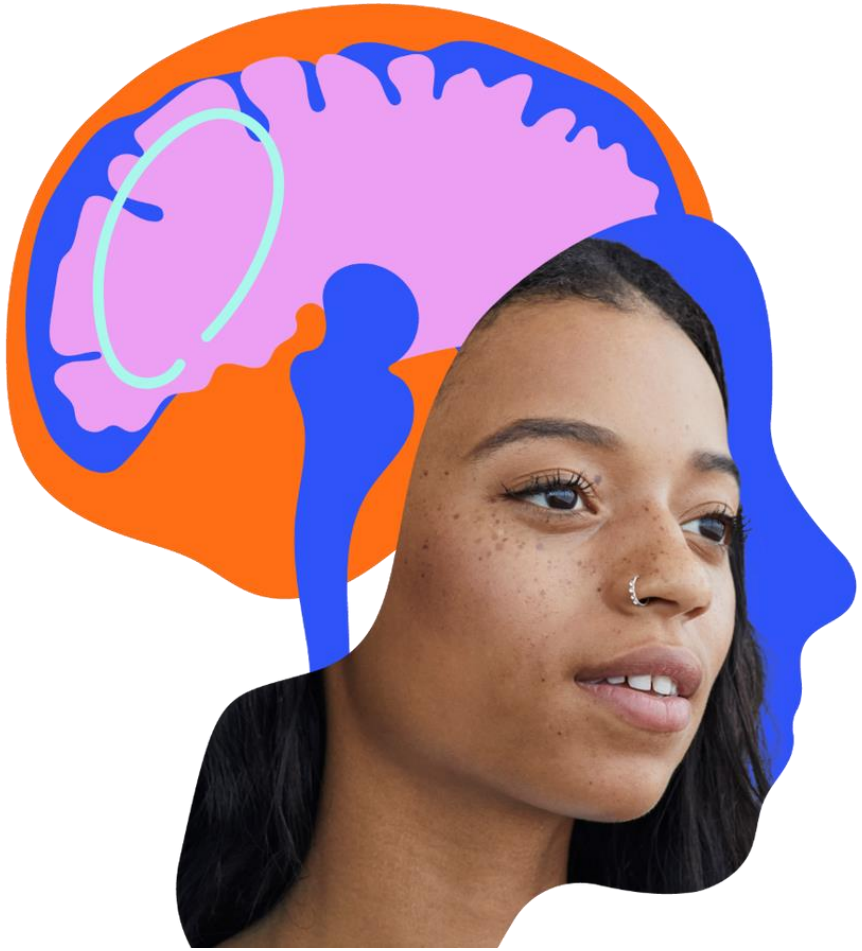
# Safe Harbor Statement

- 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,” “expect,” “plan,” “anticipate,” “believe,” “estimate,” “project,” “intend,” “future,” “opportunity”, “goal”, “potential,” or “continue,” and other similar expressions. Forward-looking statements in this presentation include statements regarding: our views and expectations regarding revenues from sales of ZULRESSO; our clinical development plans and expected timelines; the potential regulatory pathways for zuranolone; the potential of our product candidates; our expectations with respect to 2020 operating expenses and year-end cash; our belief that existing cash will support operations into 2022; our belief in the potential of our product candidates in various indications; the potential profile and benefit of our product candidates; our estimates as to the number of patients with disorders and diseases of interest to us; and the goals, opportunity and potential for our business. 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:
    - the impact of the COVID-19 pandemic on sales of ZULRESSO may last longer than we expect or may reoccur in waves; our post-restructuring focus on geographies where there are existing, active ZULRESSO treating sites may not be sufficient for us to achieve success from sales of ZULRESSO or to generate revenues at meaningful levels or at levels necessary to justify our investment even after the impact of the COVID-19 pandemic lessens; we may not be able to overcome the barriers to treatment with ZULRESSO or we may continue to encounter other issues or challenges in commercializing ZULRESSO which could further limit the potential of ZULRESSO and the timing and amount of future revenues; we may never be able to generate meaningful revenues from sales of ZULRESSO or to generate revenues at levels necessary to justify our investment; results achieved with use of ZULRESSO in the treatment of PPD in commercial use may be different than observed in clinical trials, and may vary among patients.
    - we may not be successful in our development of any of our product candidates in any indication we are currently pursuing or may in the future pursue; success in pre-clinical studies or in prior 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; interim results may not be predictive of final results; and future non-clinical and clinical results for our product candidates may 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 review or approval, despite prior regulatory advice, and regulatory authorities may ask for additional trials or data.
    - we may not be able to mitigate the impact of COVID-19 on our clinical development timelines and the impact may be more significant than we expect and may negatively impact expected site initiation, enrollment, conduct or completion of our clinical trials, or cause us to pause trials or not be able to use data, in each case which may significantly impact our ability to meet our expected time-lines or may significantly impact the integrity or sufficiency of the data from our trials or increase our costs or cause us to have to change our plans; we may experience slower than expected enrollment in our clinical trials for other reasons 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.
    - we may encounter unexpected safety or tolerability issues with respect to any of our product candidates or marketed products; we may encounter different or more severe adverse events at the higher doses or in new indications we are studying in new trials; we may encounter issues with the efficacy or durability of short-term treatment, or co-initiated treatment with zuranolone or safety and efficacy concerns with respect to retreatment that require additional studies be conducted;
    - the FDA may ultimately decide that the design or results of our completed and planned clinical trials for any of our product candidates, even if positive, are not sufficient to file for or obtain regulatory approval in the indications that are the focus of our development plans; other decisions or actions of the FDA or other regulatory agencies may affect the initiation, timing, design, size, progress and cost of clinical trials and our ability to proceed with further development; we may encounter technical and other unexpected hurdles in the development and manufacture of our product candidates which may delay our timing or change our plans or increase our costs;
    - the internal and external costs required for our ongoing and planned activities, and the resulting impact on expense and use of cash, may be higher than expected which may cause us to use cash more quickly than we expect or change or curtail some of our plans or both; our expectations as to expenses, year-end cash and cash needs may prove not to be correct for other reasons such as changes in plans or actual events being different than our assumptions; we may be opportunistic in our future financing plans even if available cash is sufficient; 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;
    - 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; and
    - We 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 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.
- 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.

Sage Therapeutics™

# Who We Are: Sage Therapeutics

- Developing innovative treatment options with the potential to transform the lives of people with brain health disorders
- We continue to advance an industry-leading pipeline of novel brain health assets:
  - **First and only** product approved specifically for postpartum depression
  - **5** NCE clinical candidates across **10** potential indications
  - In-house library of **>6K** proprietary compounds
  - **$671M** cash-on-hand as of September 30, 2020



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*Abbreviations: NCE = new chemical entity*

# A Leading Brain Health Portfolio


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*Light shades indicate trials in the planning or evaluation stage*

# Depression Franchise

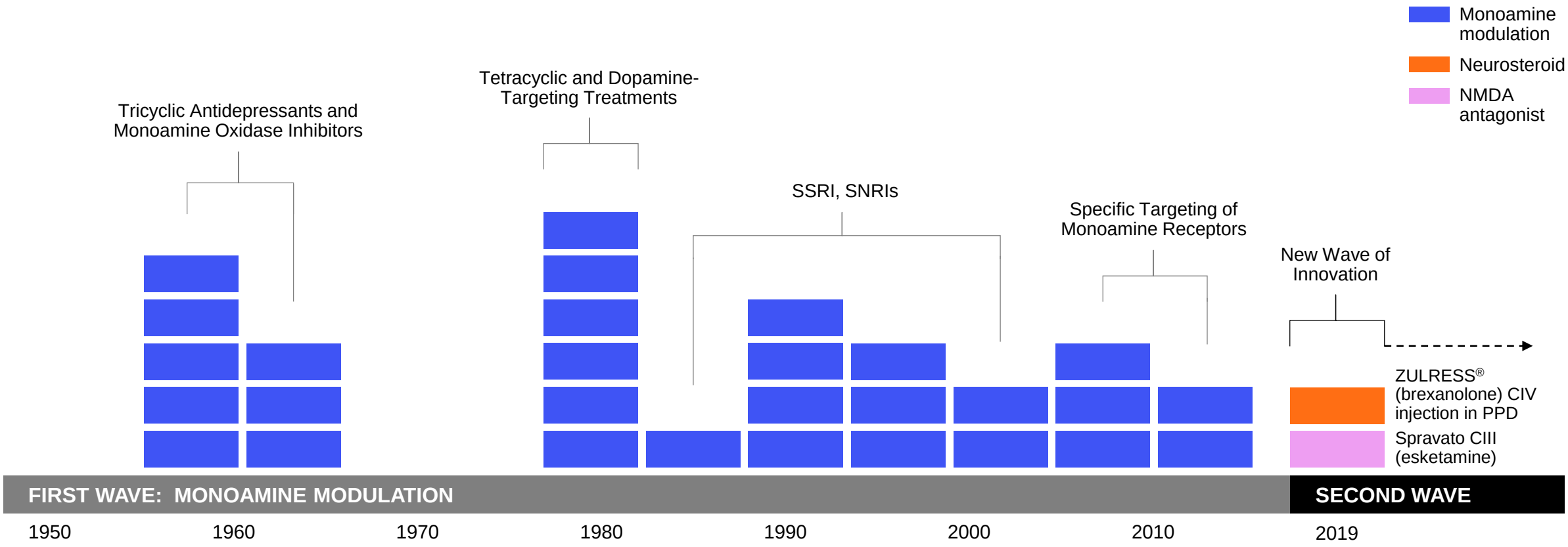
# Psychiatry as Medicine

Our goal is to develop medicines to treat depression with potentially unique efficacy and tolerability profiles that:

- Allow treating-as-needed
- Act rapidly
- Reduce stigma

# Sage Leading Second Wave of Neuropsych Innovation

*First new MOA in 60 years*

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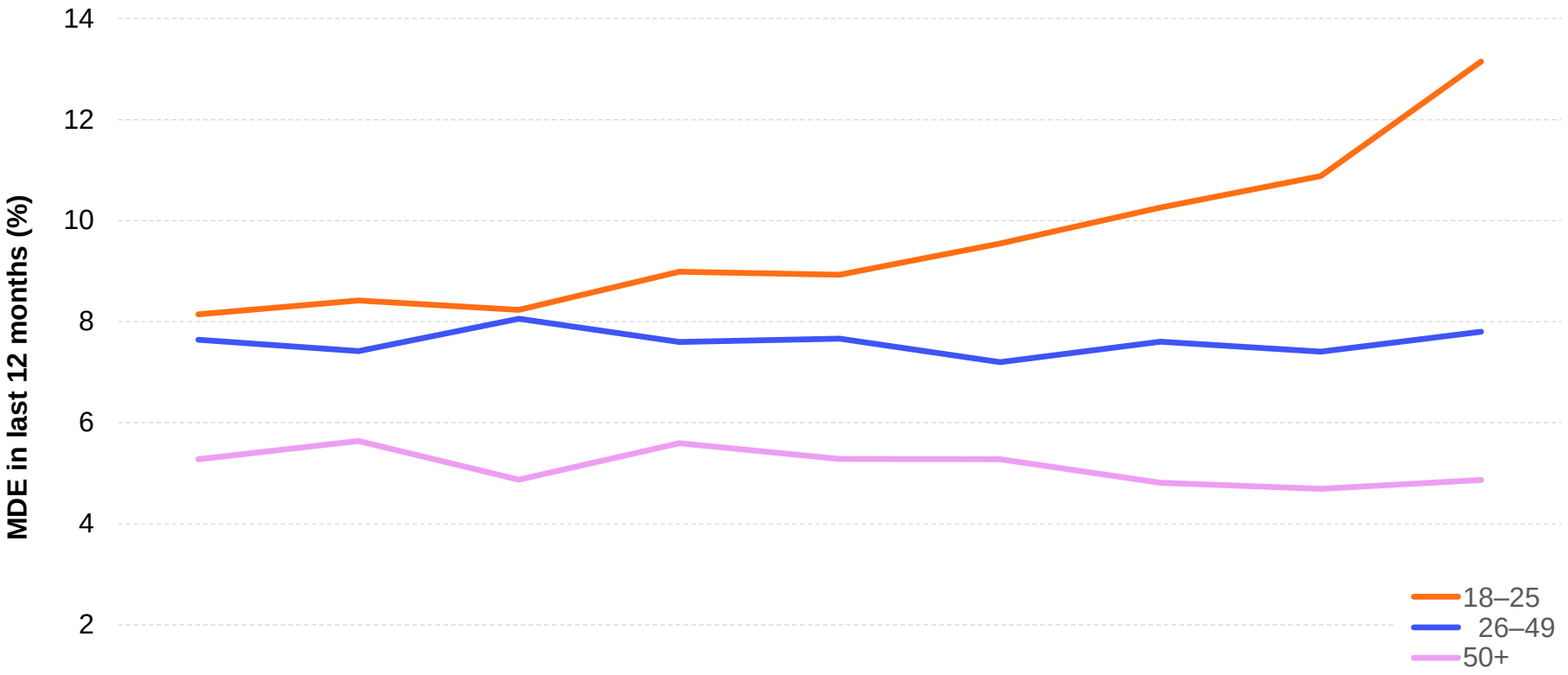
*Source: Thomas, D., & Wessel, C. (2017). The State of Innovation in Highly Prevalent Chronic Diseases: Volume I: Depression Therapeutics. BIO.*

# Depression Remains an Area of Significant Unmet Need, Reflecting Lack of Innovation




Despite substantial increases in therapies for depression during the first wave (i.e., monoamine modulation), rates of major depressive episodes (MDE) have increased from 2009 to 2017

**FIRST WAVE: MONOAMINE MODULATION** | **SECOND WAVE**

2009 2017 2019

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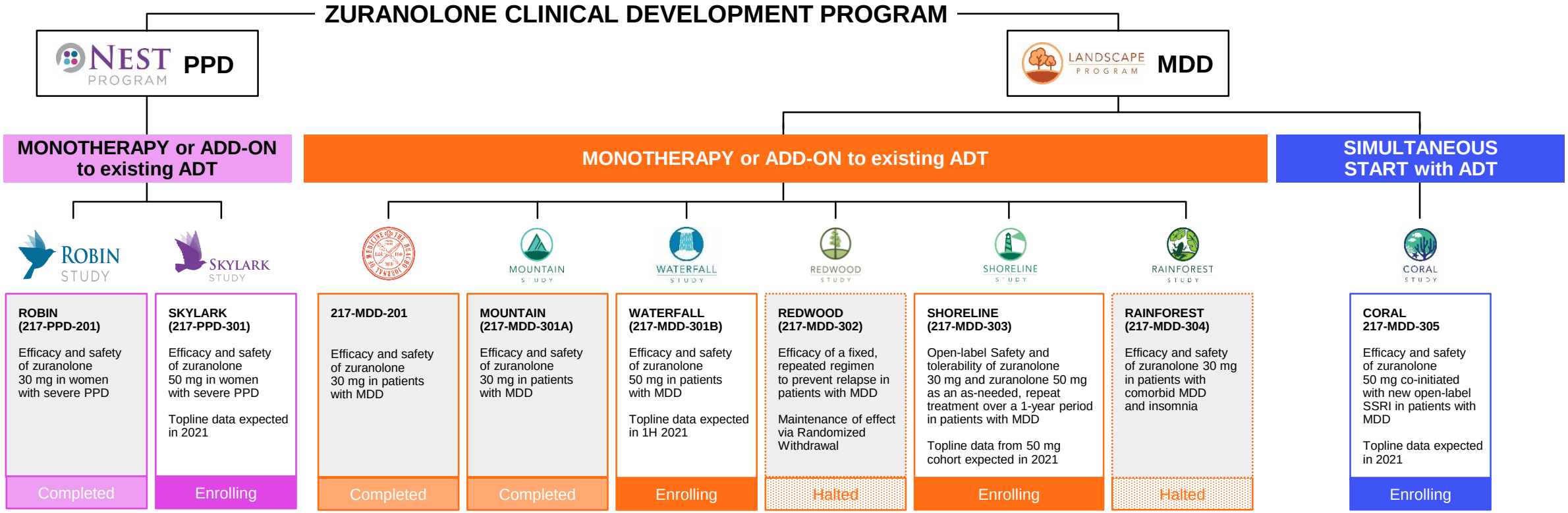
*Sources: J Abnorm Psychol. 2019 Apr;128(3):185-199. doi: 10.1037/abn0000410. Epub 2019 Mar 14.*

# Zuranolone's (SAGE-217) Landscape Program

*Potential to reshape the depression landscape*




MDD=major depressive disorder; PPD=postpartum depression.

1. Kanes SJ et al. Lancet. 2017;390(10093):480-489. 2. Meltzer-Brody et al. Lancet. 2018;392(10152):1058-1070. 3. Sage Therapeutics, Inc. Data on file. 4. Gunduz-Bruce, et al. N Engl J Med 2019; 381:903-911.

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# Zuranolone Development Plan

*If Successful, Potential to Pursue an Efficient and Expedited Pathway to Filing*

Top-line data from studies to support these pathways expected in 2021

**ORAL PPD THERAPY**

SKYLARK (PPD-301)

- Women with PPD, 14-day course of zuranolone

**AS NEEDED THERAPY IN PATIENTS WITH MDD**

WATERFALL (MDD-301B)

- People with MDD, 14-day course of zuranolone
- Long term safety data, including from maintenance study, expected to be required for US label

**ACCUTE RAPID RESPONSE (RRT)** in MDD when coinitiated with new ADT

CORAL (MDD-305)

- People with MDD, 14-day course of zuranolone

Sage is also currently evaluating the ongoing zuranolone clinical pharmacology and safety program and plans to finalize requirements to support a potential future NDA with the FDA

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Abbreviations: PPD = Postpartum Depression, MDD = Major Depressive Disorder, ADT = Antidepressant Therapy

# ZULRESSO® (brexanolone) CIV Injection

*Commercial efforts primarily focused on geographies that have existing, active treating sites*

- **Support in existing geographies:** Primary focus on working with healthcare providers and supporting women with PPD in geographies with active ZULRESSO treating sites


- **Customized case management:** Sage Central, Sage's national patient support center, continuing to provide customized case management support to women with PPD

SAGE CENTRAL™
PATIENT SUPPORT

**Please see Boxed Warning and Important Safety Information**

ZULRESSO is only available at certified healthcare settings through a restricted program called the ZULRESSO REMS due to the risk of serious harm resulting from excessive sedation or sudden loss of consciousness

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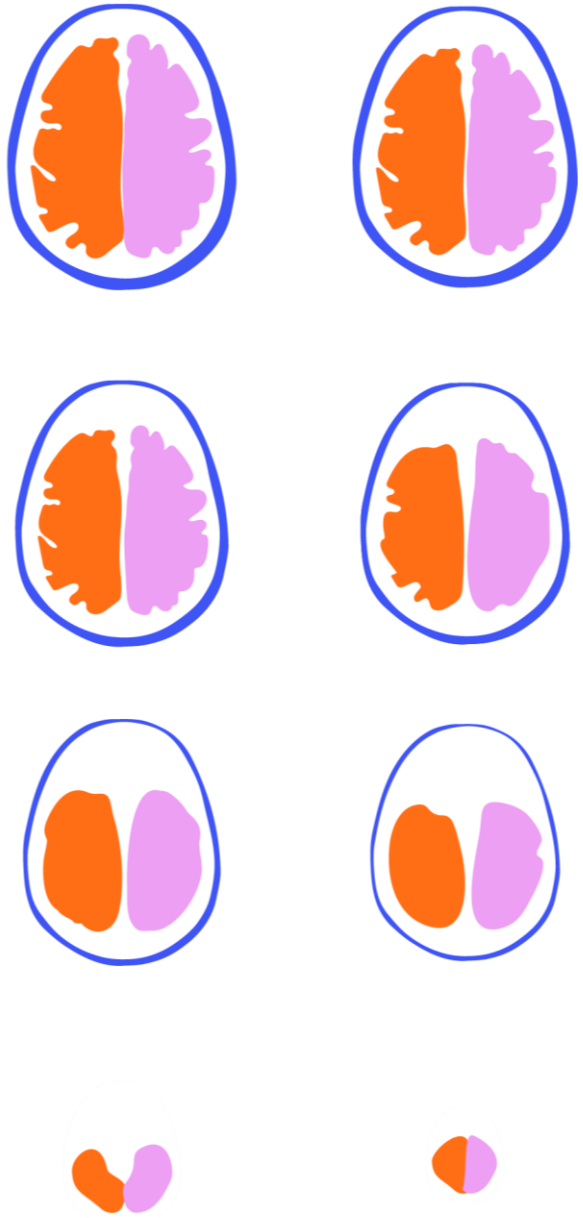
# Neurology Franchise

# Next-generation Asset Being Evaluated for Neurological Conditions

- **SAGE-324**
  - Novel next-generation positive allosteric modulator (PAM) of $GABA_A$ receptors
  - Chronic dosing: long half-life provides consistent plasma concentrations with minimal daily fluctuations after multiple doses
  - Potential therapy for neurological conditions, such as essential tremor, epilepsy and Parkinson's disease



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# SAGE-324 in Essential Tremor

## *Ongoing Phase 2 placebo-controlled study*

**Essential tremor (ET) is the most common movement disorder where standard of care may be inadequate for many**

- Symptoms progressively worsen over time and can significantly impair activities of daily living and independence
- Patients with tremor resulting in impaired functioning or disability are treated with pharmacotherapeutic interventions[1]
- Approximately 50% of diagnosed patients receive pharmacotherapy for ET[2]

**SAGE-324 well-suited for development in ET**

- Pathophysiology of ET is associated with reduced GABAergic tone in regions of the brain controlling motor function – GABA PAMs mechanistically have the potential to address that deficit by improving GABA receptor function
- Long half-life supports low peak-to-trough ratio and provides flexibility in dosing paradigms – potentially beneficial for ET where stable levels are a clinical challenge

**Estimated**

**6M+ people have ET** in the U.S.

**Yet only about**

**20% of**

people with ET seek treatment[3]

Medications are generally effective in about

**50%**

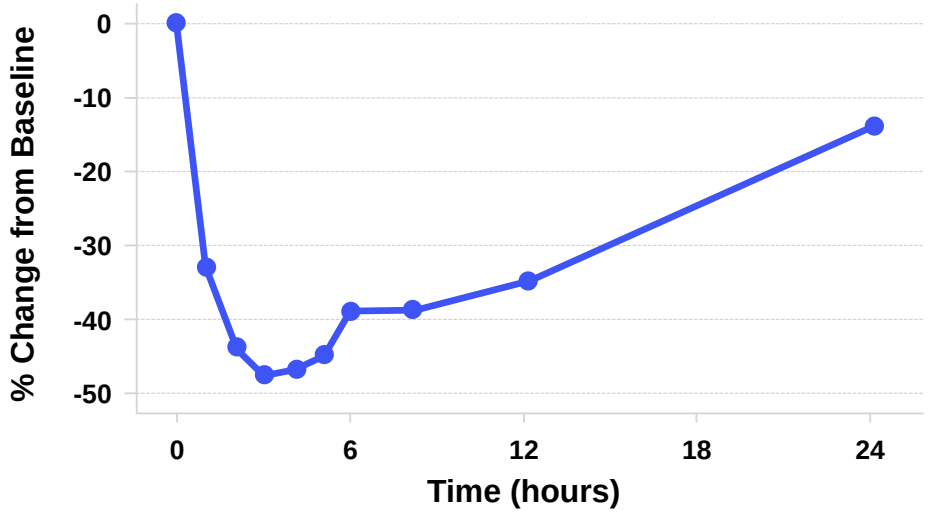
of patients who seek treatment[4]

*1. Rajput AH, Rajput A. Medical treatment of essential tremor. Journal of Central Nervous System Disease 2014:6. 2. Louis ED. Medication non-adherence in essential tremor. Parkinsonism Relat Disord. 2015 February ; 21(2): 138–141. 3. MLIB-2278. Data on file: US ET Prevalence. 4. Thanvi B, Lo N, Robinson T. Essential tremor-the most common movement disorder in older people. Age and Ageing. 2006;35:344q–349*

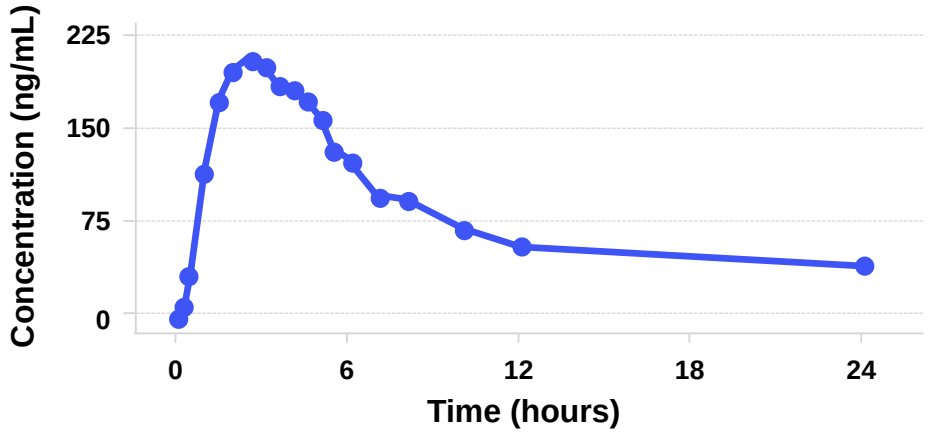
# SAGE-324: Strong PK/PD Relationship in ET

- Six patients with essential tremor received a single dose of 60mg SAGE-324
- Tremor amplitude measured using the Kinesia accelerometer and the TETRAS Performance Scale
- A clear PK/PD relationship was demonstrated
- SAGE-324 was well-tolerated in ET patients in the trial

**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**

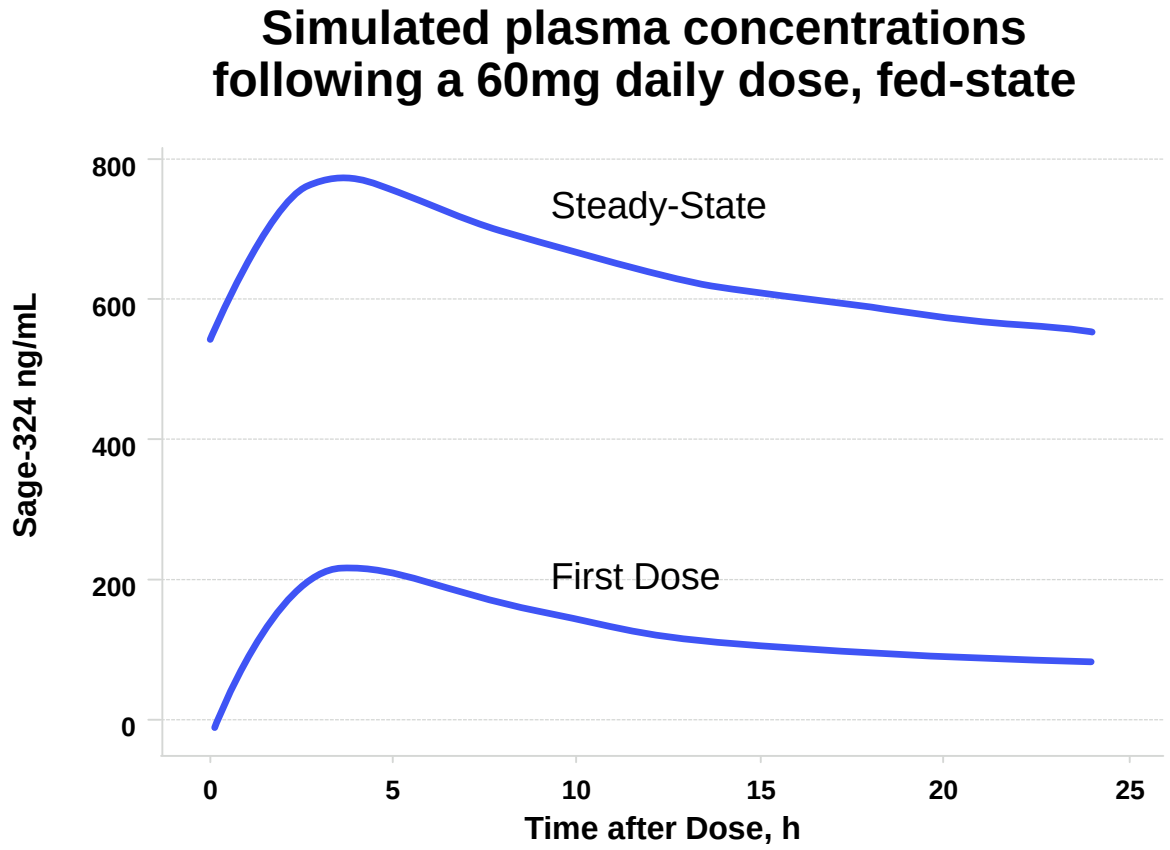



SAGE-324 was well-tolerated in Phase 1 studies; most common AEs (≥5%) included somnolence, dizziness, and feeling of relaxation

# SAGE-324: Ability to Maintain Plasma Concentrations Throughout the Dose Interval

SAGE-324 has attributes that support the potential for chronic oral dosing:

- Good oral bioavailability
  - Permits a formulation strategy that optimizes PK profile
- Long half-life
  - Consistent exposures during the dose interval
  - Diminished effect on exposure of missed or late doses
  - Gradual approach to steady state allows potential to facilitate down-titration if tolerability issues arise



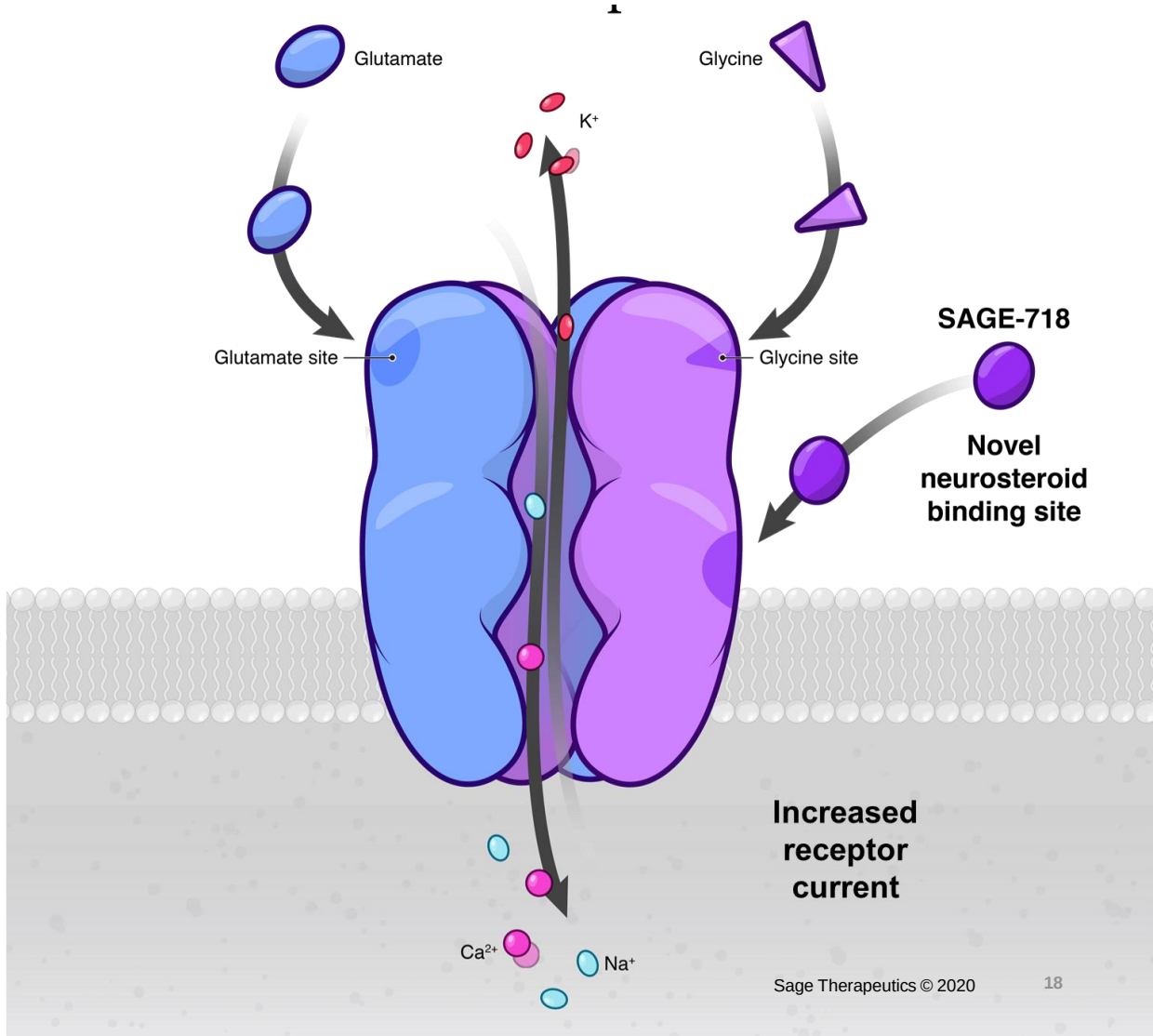

SAGE-324 was well-tolerated in Phase 1 studies; most common AEs (≥5%) included somnolence, dizziness, and feeling of relaxation

# Neuropsychiatry Franchise

# Sage's First-in-Class NMDA PAM

- NMDA receptors are thought to play a key role in a host of cognitive and behavioral processes
- Sage identified an endogenous modulator of the NMDA receptor (24S-hydroxycholesterol)
  - Yields potential biomarkers for activity and drug development
- Sage has built a library of thousands of novel 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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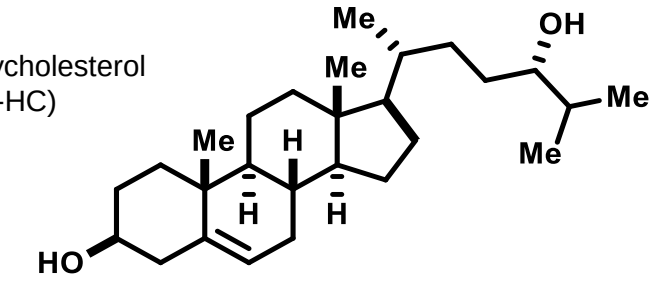
# Sage Has Developed a Robust Library of NMDAr Modulators

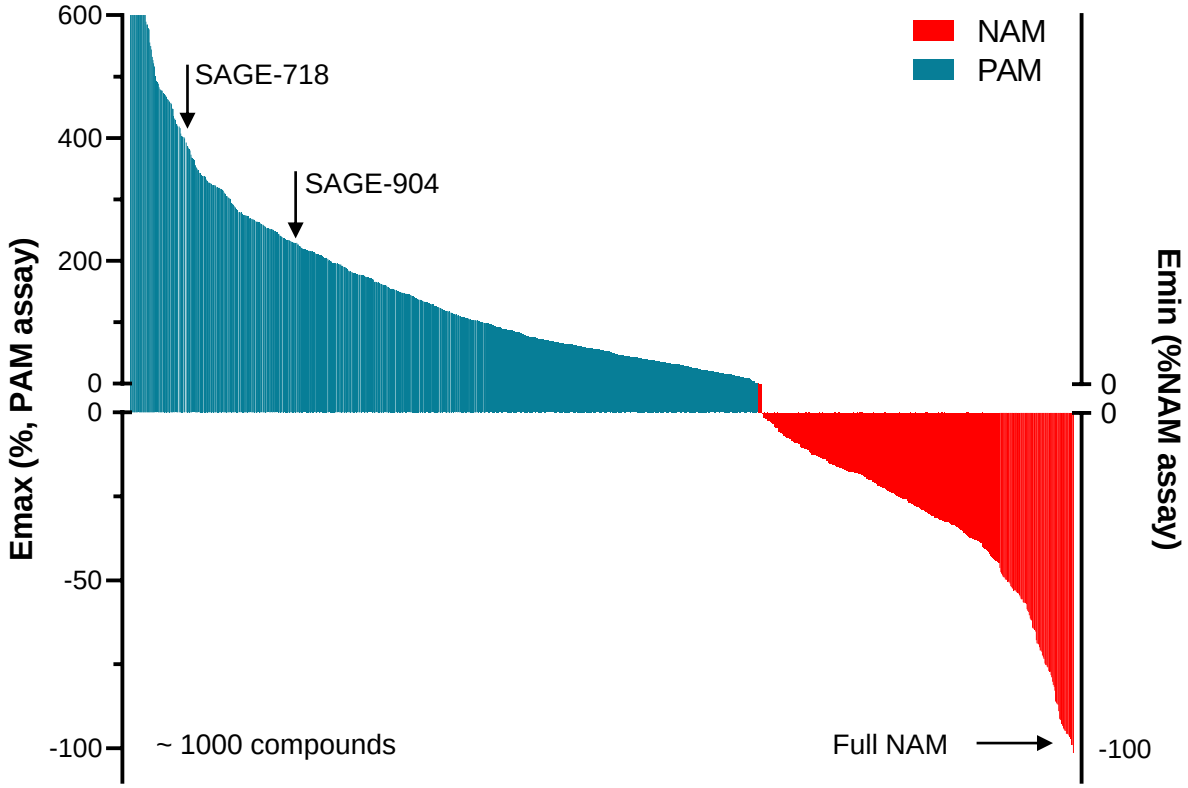
## Creating a portfolio of drug-like molecules targeting NMDA receptors

24S-hydroxycholesterol
(24S-HC)




| | | 24S-HC Endogenous | SGE-301 Research Tool | SAGE-718 Clinical | SAGE-904 Clinical |
|---|---|---|---|---|---|
| **Pharmacology** | EC50 | 220 nM | 480 nM | <100 nM | ~100 nM |
| | Emax | 160% | 220% | > 400% | < 400% |
| **Drug-like Properties** | | Poor | Poor | Good | Good |

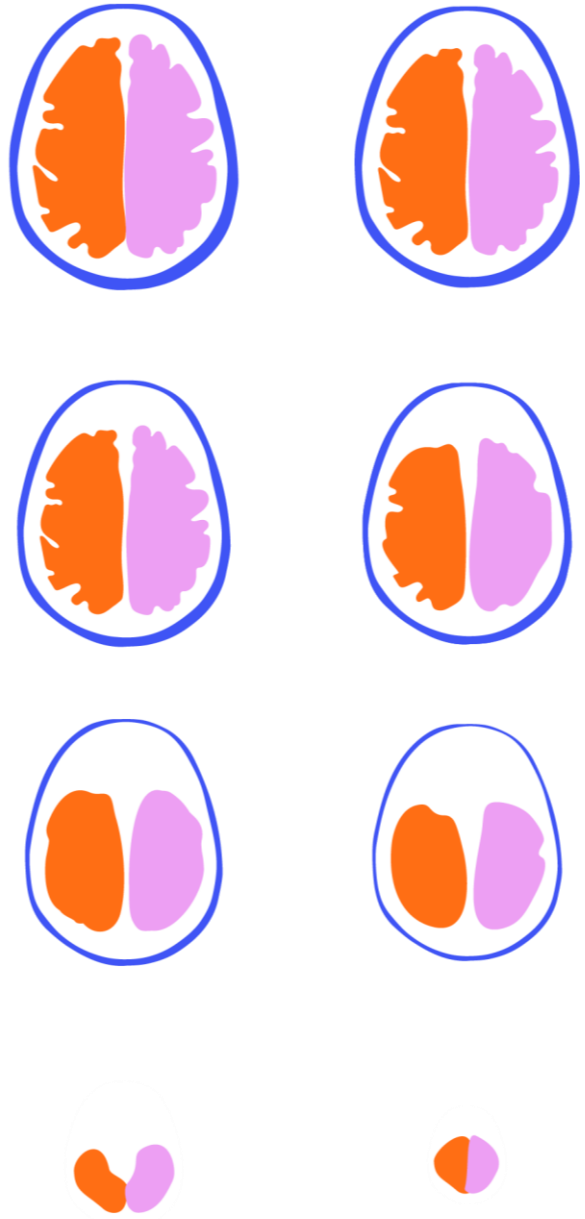
## Robust library of novel oxysterol-based NMDA modulators, with unique profiles



# 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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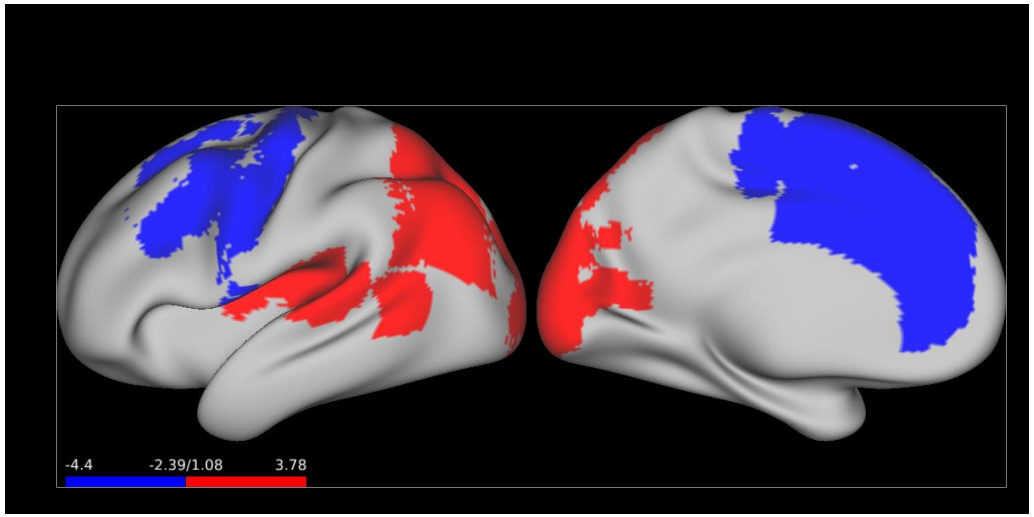
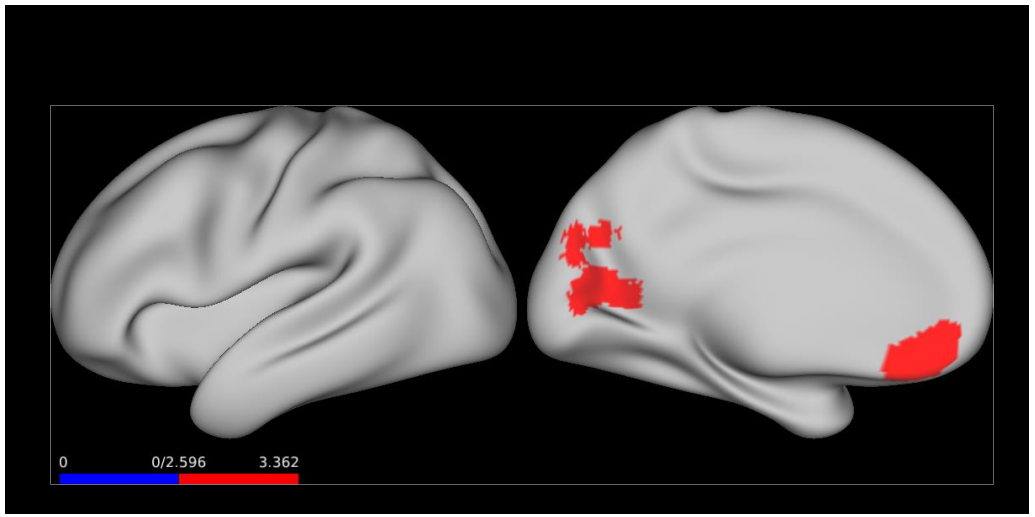
# SAGE-718 Attenuated Effects of Ketamine on Brain Circuits, in Phase 1 Study

## 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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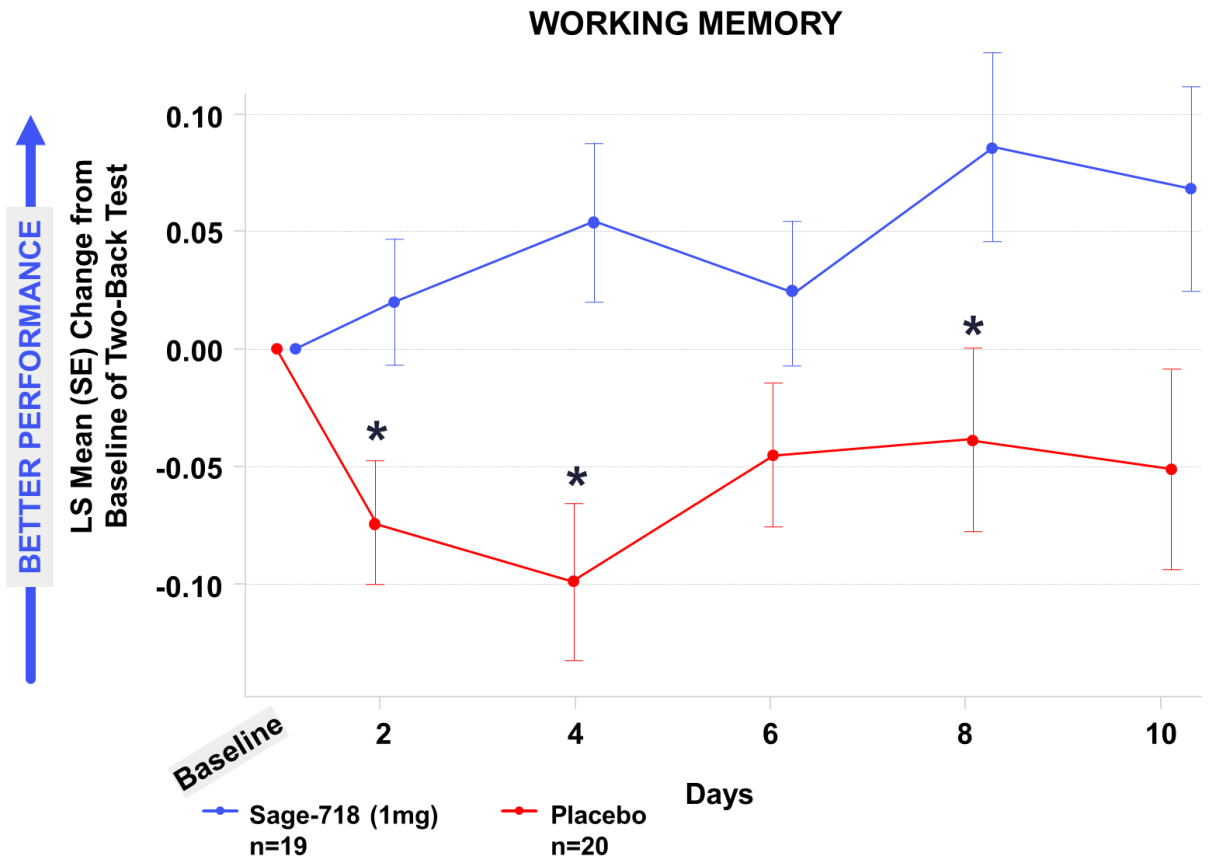
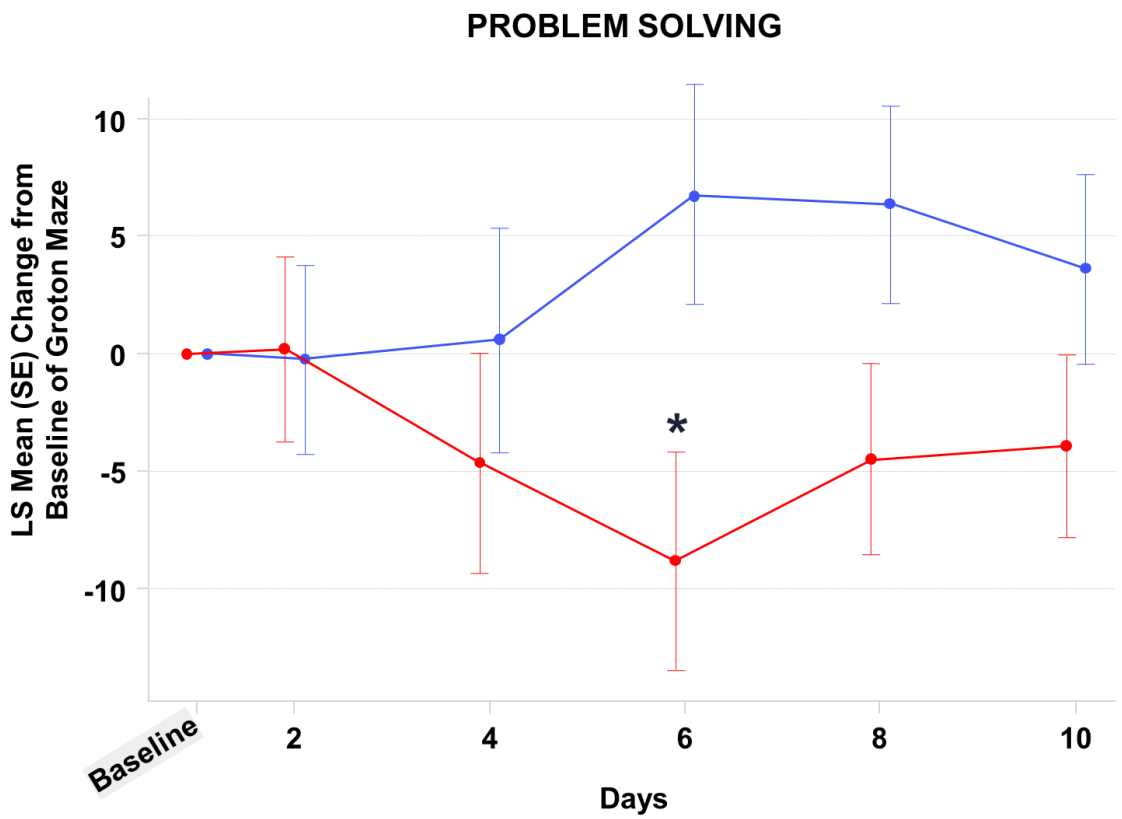
# In a Phase 1 Study with Healthy Volunteers SAGE-718 Significantly Improved Executive Functioning

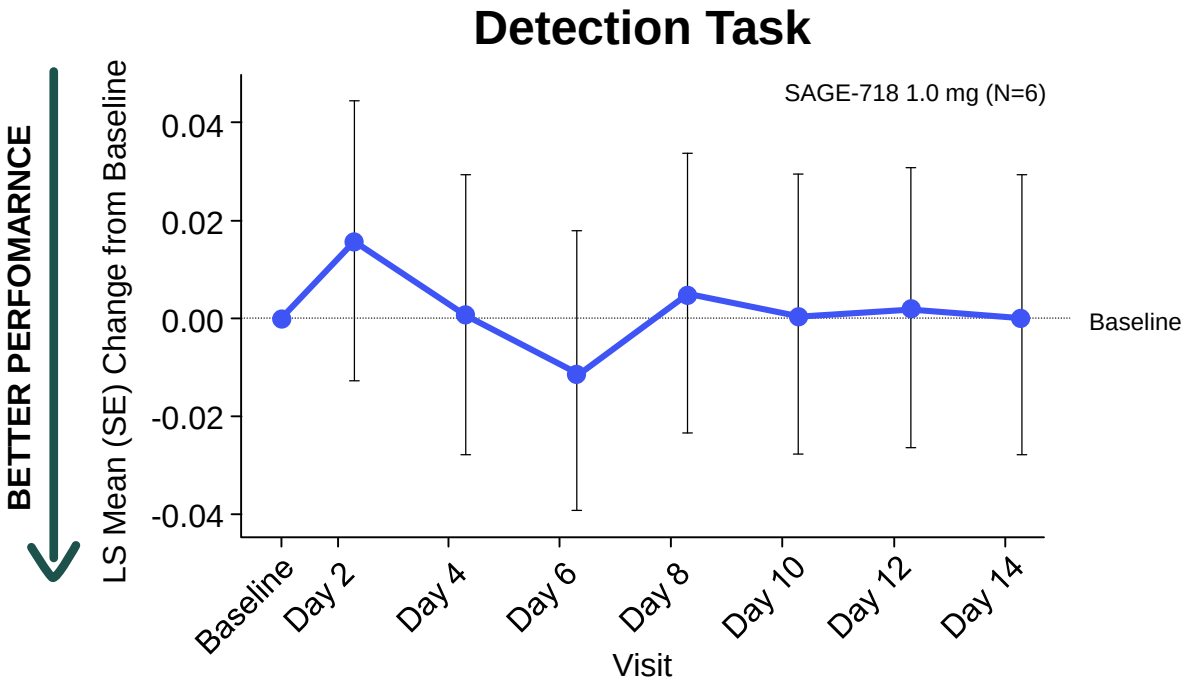


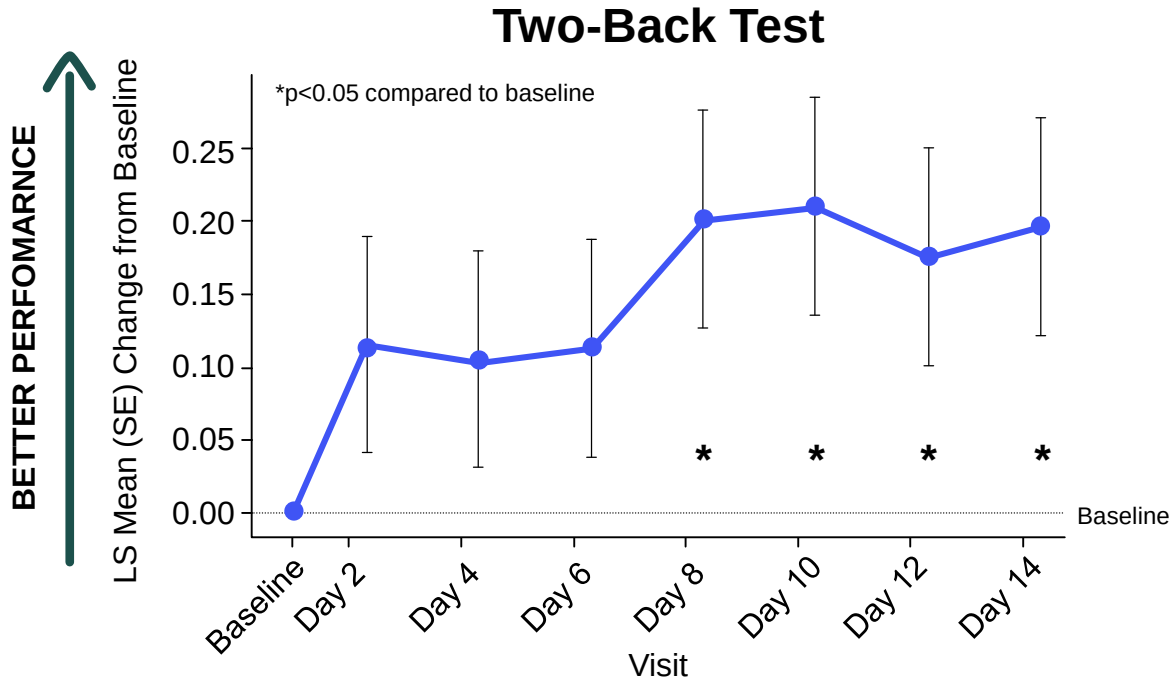




*p<0.05. A MMRM model was applied with change from baseline in each cognitive assessment test score as the response variable and treatment, visit, visit-by-treatment interaction as fixed effect, baseline as covariate, and measurements within the same subject as repeated measure. Unstructured covariance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

In Phase 1 studies of SAGE-718 no serious adverse events or deaths have occurred, and most treatment-emergent adverse events have been mild in severity.

# Cognitive Performance in Patients w/ Early HD Treated with Open-Label Sage-718 Over 2 Weeks




| VARIABLE | MEAN (SD) | RANGE |
|---|---|---|
| Total Functional Capacity | 11.3 (2.87) | (7, 13) |
| Baseline MoCA | 23.3 (4.99) | (16, 27) |
| UHDRS Motor Score | 7.5 (5.26) | (0,12) |

Subjects had mild to moderate disease (HD1 or HD2, defined by TFC) and cognitive impairment at baseline

In Phase 1 studies of SAGE-718 no serious adverse events or deaths have occurred, and most treatment-emergent adverse events have been mild in severity.

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# Third Quarter 2020 Financial Results

*Strong financial position with $671M in cash*

| Item | Q3 '20 | Q3 '19 |
|---|---|---|
| Revenue:<br>• *Zulresso*<br>• *Collaboration* | $1.6M<br>• *1.6M*<br>• *-* | $3.6M<br>• *1.5M*<br>• *2.1M* |
| R&D Expense | $74.1M | $102.1M |
| SG&A Expense | $35.1M | $88.5M |
| Cost of Goods Sold | $0.1M | $0.1M |
| Total Operating Costs and Expenses | $108.8M | $190.7M |
| Net Loss | ($105.7M) | ($180.0M) |
| Cash and Marketable Securities | $671M | $1.1B |

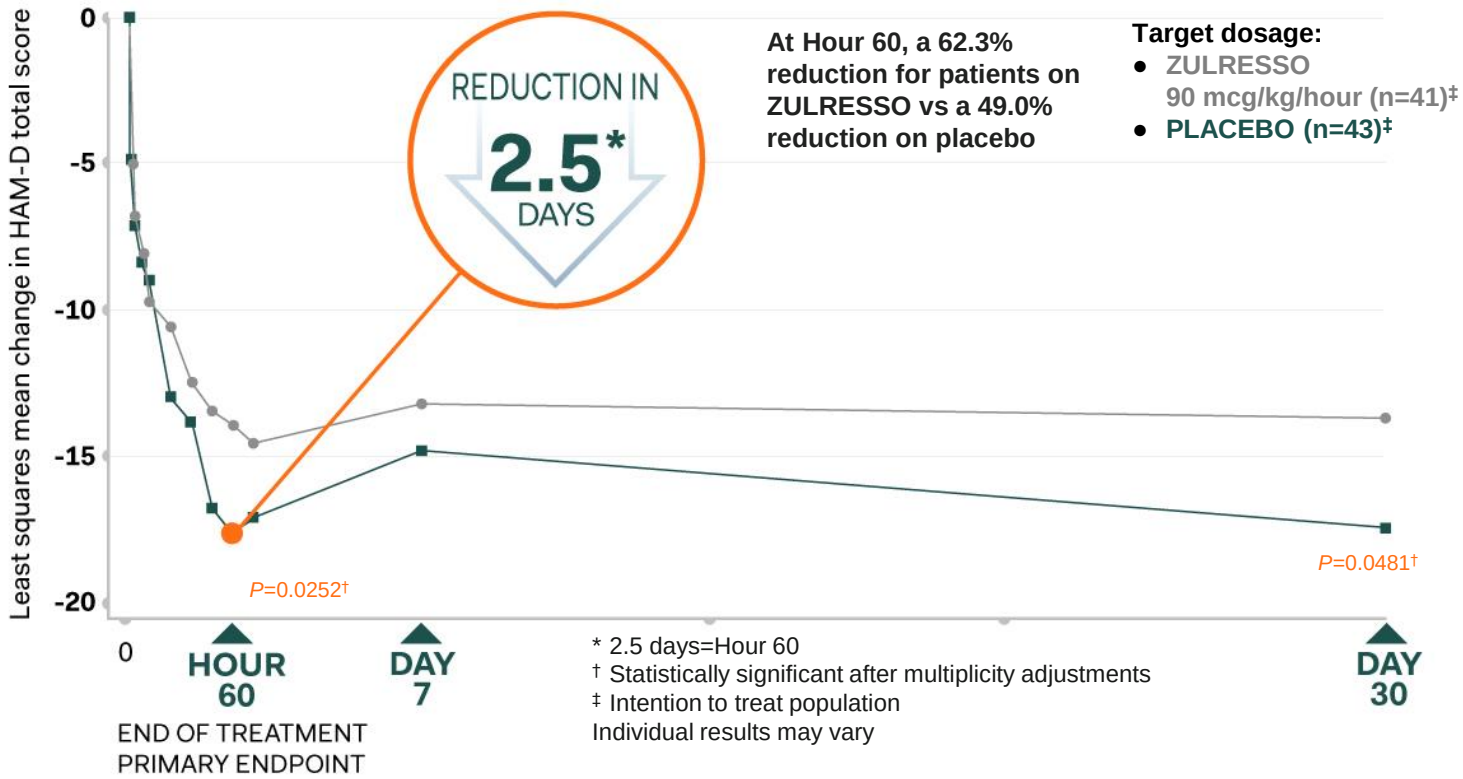
- Sage anticipates a cash balance of at least $550 million at end of 2020, which the Company anticipates will support operations into 2022, based on current operating plans.

# Appendix

# ZULRESSO® (brexanolone) CIV Injection

*Treated patients experienced rapid improvement of depressive symptoms*

**Change from baseline in HAM-D total score over time in Study 1 with the recommended target dosage of ZULRESSO (90 mcg/kg/h)[i,ii]**




**Durable therapeutic effect**

A prespecified secondary efficacy endpoint was the mean change from baseline in HAM-D total score at Day 30[i]

In Study 1, significantly greater symptom reduction vs placebo was observed at Day 30[i,ii]

In Study 2, the 90 mcg/kg/hour arm maintained therapeutic effect at Day 30, but did not show a greater reduction vs placebo

**The most common adverse reactions** (incidence of ≥5% and at least twice the rate of placebo):

- Sedation/somnolence
- Dry mouth
- Loss of consciousness
- Flushing/hot flush

ZULRESSO is only available through the ZULRESSO Risk Evaluation and Mitigation Strategy (REMS), a safety program to manage the risk of serious harm resulting from excessive sedation and sudden loss of consciousness during the ZULRESSO infusion. To administer ZULRESSO, sites of care must be certified in the ZULRESSO REMS[iii]

**Please see full Prescribing Information, including Boxed Warning available with this presentation**

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*Sources: i. ZULRESSO Prescribing Information. Cambridge, MA: Sage Therapeutics, Inc., ii. Meltzer-Brody S et al. Lancet. 2018;392(10152):1058-1070, iii. ZULRESSO REMS. https://zulressorems.com/#Public*

# ZULRESSO® (brexanolone) CIV Injection

*Boxed warning*

**WARNING: EXCESSIVE SEDATION AND SUDDEN LOSS OF CONSCIOUSNESS**

*See full prescribing information for complete boxed warning.*

- Patients are at risk of excessive sedation or sudden loss of consciousness during administration of ZULRESSO. (5.1)
- Because of the risk of serious harm, patients must be monitored for excessive sedation and sudden loss of consciousness and have continuous pulse oximetry monitoring. Patients must be accompanied during interactions with their child(ren). (5.1)
- ZULRESSO is available only through a restricted program called the ZULRESSO REMS. (5.1, 5.2)

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# ZULRESSO® (brexanolone) CIV injection

## *Select Important Safety Information*

These are not all the side effects of ZULRESSO.

**ZULRESSO can cause serious side effects, including:**

- **Excessive sedation and sudden loss of consciousness.** ZULRESSO may cause you to feel very sleepy (excessive sedation) or pass out (loss of consciousness). Your healthcare provider should check you for symptoms of excessive sleepiness every 2 hours while you are awake.
  - During your infusion, tell your healthcare provider right away if you feel like you cannot stay awake during the time you are normally awake or if you feel like you are going to pass out. Your healthcare provider may lower your dose or stop the infusion until symptoms go away
  - You must have a caregiver or family member with you to help care for your child(ren) during your infusion
- Because of the risk of serious harm resulting from excessive sedation or sudden loss of consciousness, ZULRESSO is only available through a restricted program called the ZULRESSO REMS.

**ZULRESSO can cause other serious side effects, including:**

- **Increased risk of suicidal thoughts or actions.** ZULRESSO and other antidepressant medicines may increase suicidal thoughts and actions in some people 24 years of age and younger. **Pay close attention to and tell your healthcare provider right away if you have any of the following symptoms, especially if they are new, worse, or worry you:**
  - Attempts to commit suicide, thoughts about suicide or dying, new or worse depression, other unusual or sudden changes in behavior or mood
  - Keep all follow-up visits and call your healthcare provider between visits as needed, especially if you have concerns about symptoms.

**The most common side effects of ZULRESSO include:**

- Sleepiness, dry mouth, passing out, flushing of the skin or face.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**Before receiving ZULRESSO, tell your healthcare provider about all your medical conditions** including if you drink alcohol, have kidney problems, are pregnant or think you may be pregnant, or are breastfeeding or plan to breastfeed. It is not known if ZULRESSO will harm your unborn baby. If you become pregnant during treatment, talk with your healthcare provider about enrolling with the National Pregnancy Registry for Antidepressants at 1-844-405-6185.

**While receiving ZULRESSO, avoid the following:**

- Driving a car or doing other dangerous activities after your ZULRESSO infusion until your feeling of sleepiness has completely gone away
- Do not drink alcohol

**Tell your healthcare provider about all the medicines you take,** including prescription and over-the-counter medicines, vitamins, and herbal supplements. ZULRESSO and some medicines may interact with each other and cause serious side effects.

**Especially tell your healthcare provider if you take** other antidepressants, opioids, or Central Nervous System (CNS) depressants (such as benzodiazepines).

**Please see the patient Medication Guide, including information about serious side effects, for ZULRESSO in the full Prescribing Information.**

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# Strategic Zuranolone Collaboration with Shionogi

- **Expansion of Global Footprint**
  - Goal of collaboration to accelerate development of a potentially groundbreaking medicine to patients in key Asian markets
  - Sage maintains exclusive rights to develop and commercialize zuranolone outside of those geographies
- **Expert Partner in Key Asian Markets**
  - Shionogi is responsible for clinical development and commercialization of zuranolone in Japan, Taiwan, and South Korea
  - Shionogi has strong presence in Asia in developing & commercializing therapeutics for CNS disorders
- **Attractive Terms**
  - Sage to receive tiered royalties on sales averaging in the greater than 20% range, if commercialized
  - Shionogi has also granted Sage certain rights to co-promote zuranolone in Japan across all indications

Sage Therapeutics™ + SHIONOGI

**$90M**

Upfront payment

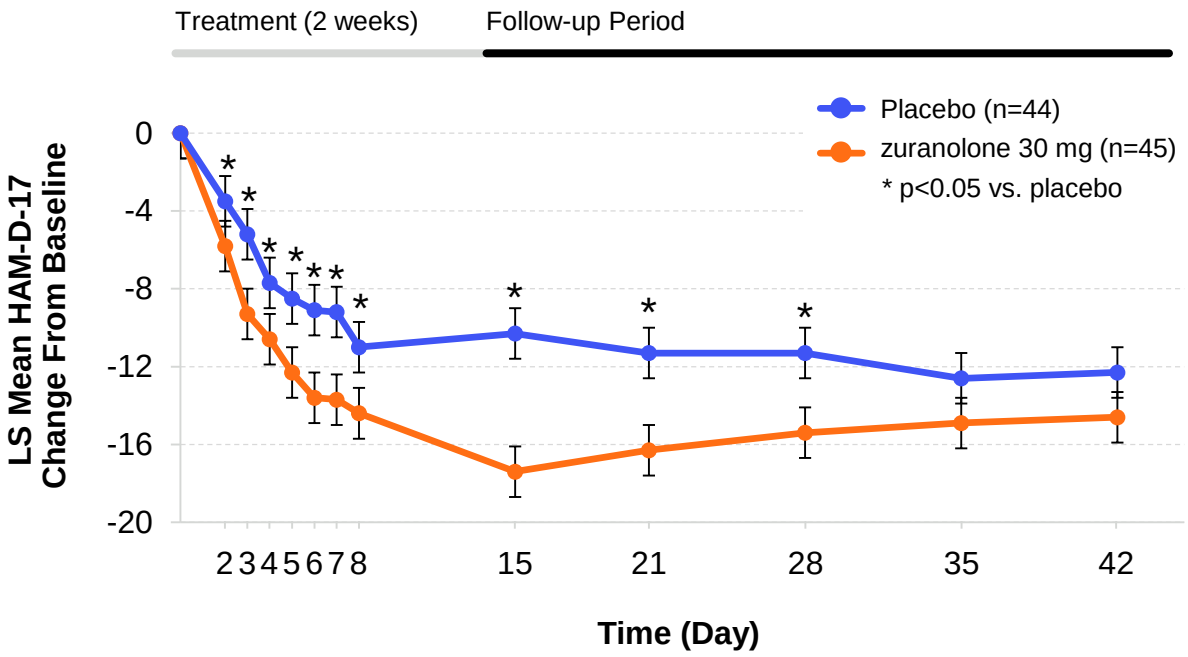
**$485M**

Potential development & commercial milestones

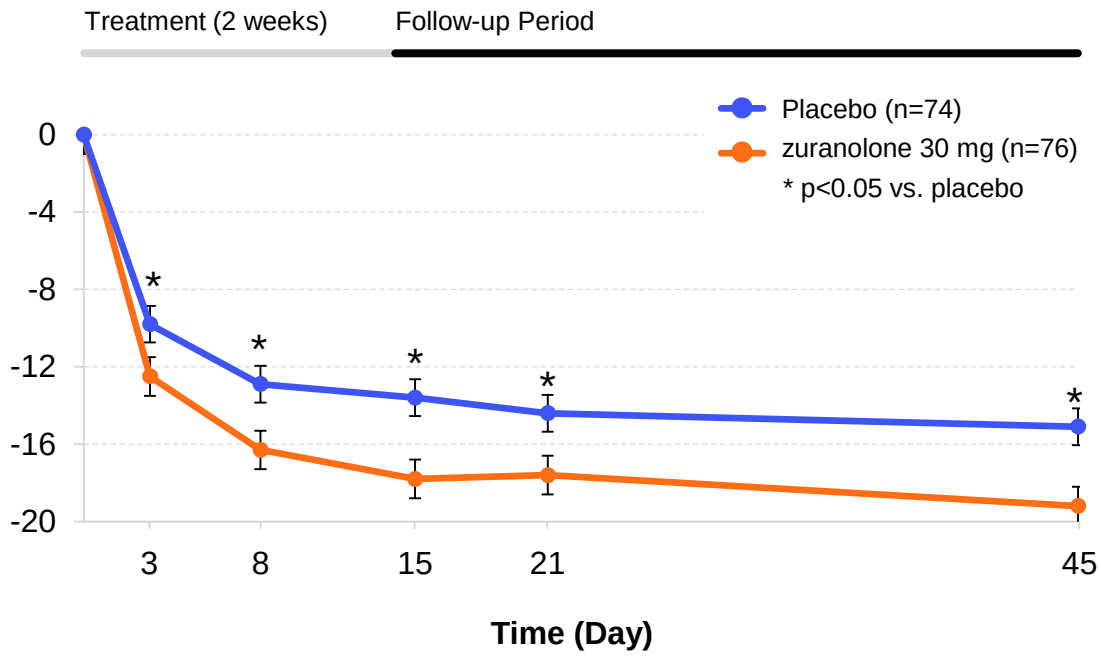
# MDD-201 & ROBIN Studies

*Rapid onset of activity with generally well-tolerated safety profile*

**MDD-201**




**ROBIN (PPD-201)**




Zuranolone was generally well-tolerated in both studies

The most common AEs (≥5%) in the MDD-201 study included headache, dizziness, nausea, and somnolence

The most common AEs (≥5%) in the PPD-201 study included somnolence, headache, dizziness, upper respiratory tract infection, diarrhea, and sedation

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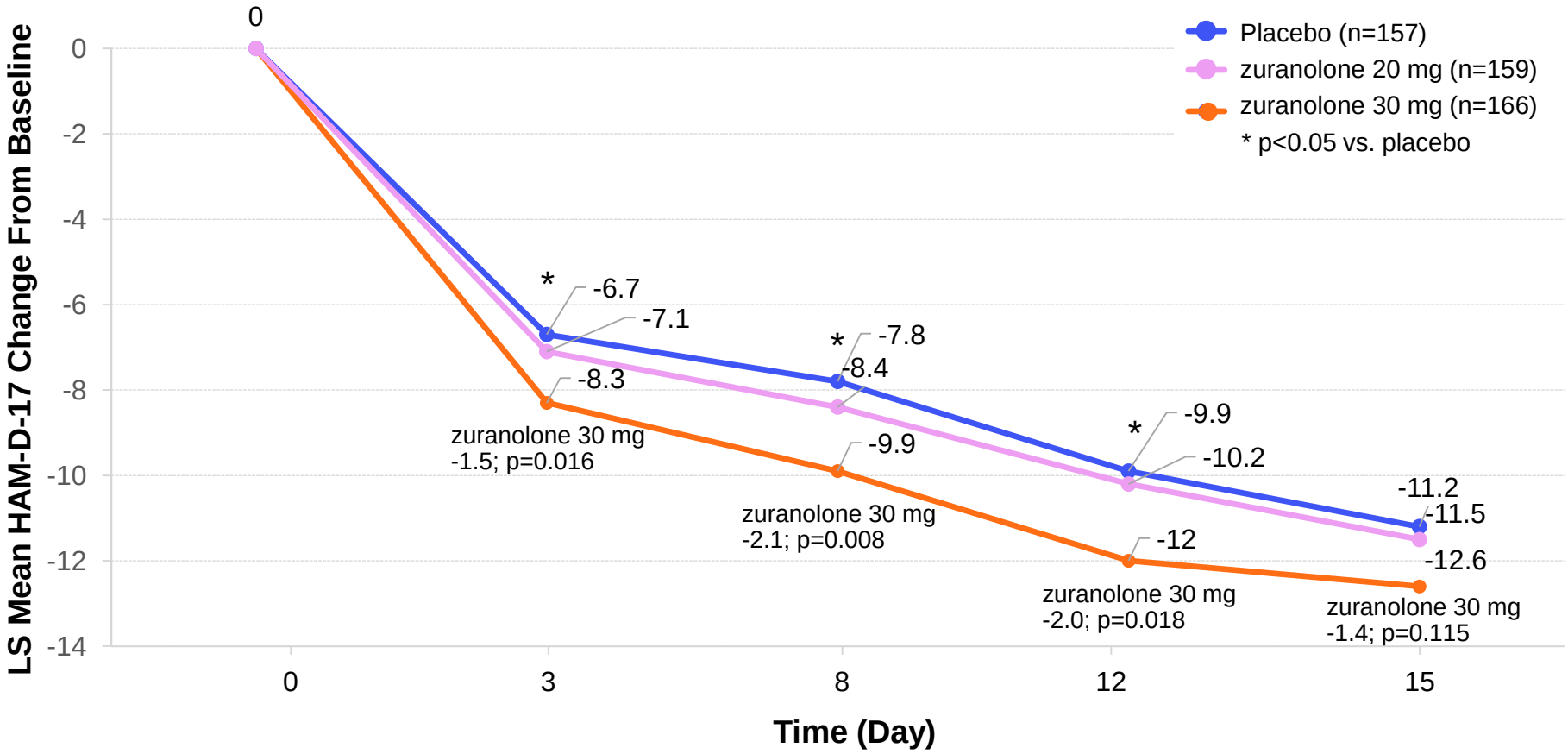
*Abbreviations: AEs = adverse events*

# MOUNTAIN (MDD-301) Study

*Displays rapid, robust onset similar to prior pivotal studies*




Zuranolone was generally well-tolerated in the study

The most common AEs (≥5%) included headache dizziness, somnolence, fatigue, diarrhea, sedation and nausea

Rapid onset of effect for zuranolone 30 mg was seen beginning at Day 3 with maintenance of effect through Day 15; statistical separation from placebo observed Days 3 – 12

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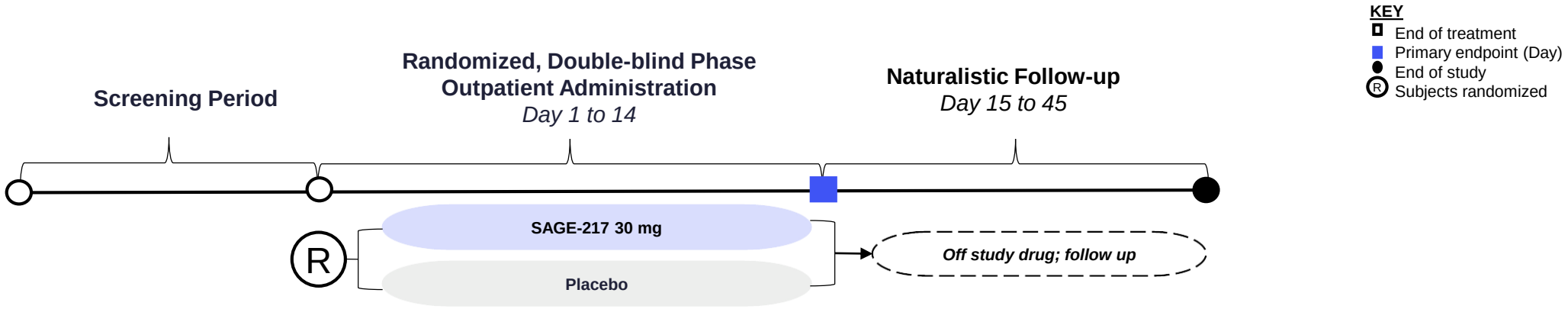
*Abbreviations: AEs: = adverse events*

# Study Design:

## Completed Studies

# **Completed** SAGE-217 Studies

*Pivotal Ph. 2 in PPD (ROBIN; PPD-201)*




**STUDY OVERVIEW**

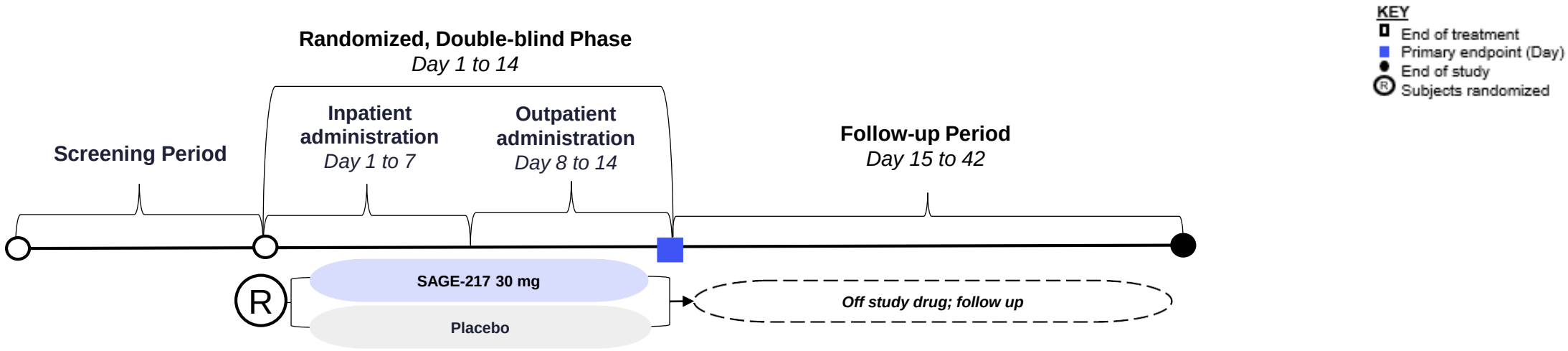
| | | | | | |
|---|---|---|---|---|---|
| **Arms** | Randomization: 1:1<br>• SAGE-217 30 mg<br>• Placebo | **Key Inclusion Criteria** | • Major Depressive Episode that began no earlier than the third trimester and no later than the first 4 weeks following delivery, as diagnosed by the SCID-I<br>• Subject is ≤ six months postpartum<br>• Ceased lactating at screening or, if still lactating or actively breastfeeding at screening, must agree to temporarily cease giving breast milk to her infant(s) | **Primary Endpoint** | • Change from baseline in HAM-D total score* |
| **Dosing Regimen** | 2-week, once-nightly | **Key Exclusion Criteria** | • Active psychosis<br>• Attempted suicide associated with current episode of PPD (Note, suicidal ideation is not an exclusion; other protocol-defined inclusion/exclusion criteria may apply)<br>• Medical history of seizures, bipolar disorder, schizophrenia, and/or schizoaffective disorder | **Secondary Endpoints** | • Safety and tolerability compared with placebo as assessed by:<br>  • Incidence of AEs, vital signs, clinical laboratory evaluations, ECG parameters**<br>  • C-SSRS** |

*During double-blind phase; **During double-blind and follow-up periods

NCT02978326. Available from: clinicaltrials.gov [accessed November 2019]

# **Completed** SAGE-217 Studies

## *Pivotal Ph. 2 in MDD (MDD-201)*




**STUDY OVERVIEW**

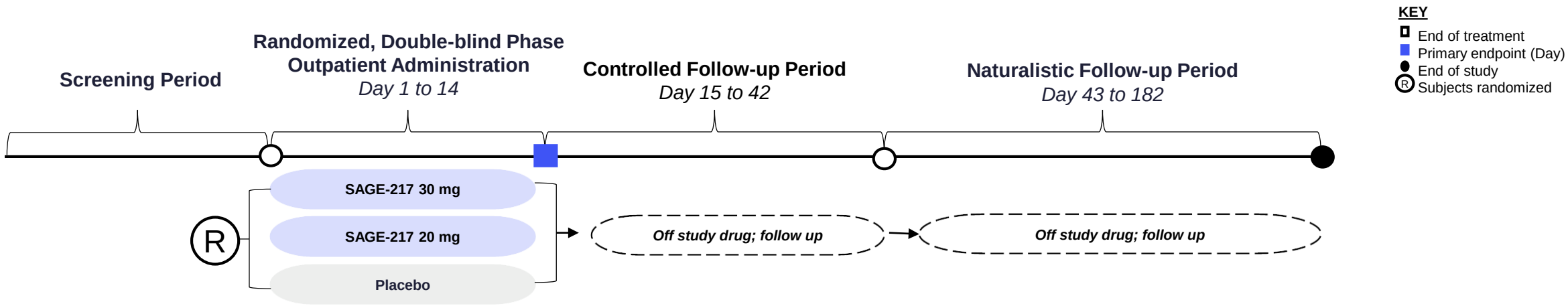
| | | | | | |
|---|---|---|---|---|---|
| **Arms** | Randomization: 1:1<br>• SAGE-217 30 mg<br>• Placebo | **Inclusion Criteria** | • Diagnosis of MDD with symptoms that have been present for at least a 4-week period | **Primary Endpoint** | • Change from baseline in HAM-D* |
| **Dosing Regimen** | 2-week, once-nightly | **Exclusion Criteria** | • History of suicide attempt<br>• Active psychosis<br>• Medical history of seizures, bipolar disorder, schizophrenia, and/or schizoaffective disorder<br>• History of treatment-resistant depression, defined as persistent depressive symptoms despite treatment with adequate doses of antidepressants from two different classes for an adequate amount of time | **Secondary Endpoints** | • Safety and tolerability of SAGE-217 as assessed by:<br>○ Frequency and severity of AE/SAE**<br>○ Physical examination**<br>○ Clinical laboratory measures, vital signs, electrocardiograms, suicidal ideation using C-SSRS*<br>○ Stanford Sleepiness Scale (SSS) score*<br>• Reduction in depressive symptoms, compared to placebo, as assessed by:<br>○ Change in the 17-item HAM-D total score from baseline at all time points**<br>○ HAM-D response, HAM-D remission**<br>○ Change from baseline in MADRS total score, HAM-A total score, at Day 15 and all other time points**<br>○ HAM-D subscale and individual item scores at all time points**<br>○ CGI-I response** |

*During double-blind phase; **During double-blind and follow-up periods

NCT03000530. Available from: clinicaltrials.gov [accessed November 2019]

# **Completed** SAGE-217 Studies

## *Phase 3 MOUNTAIN (MDD-301)*




**STUDY OVERVIEW**

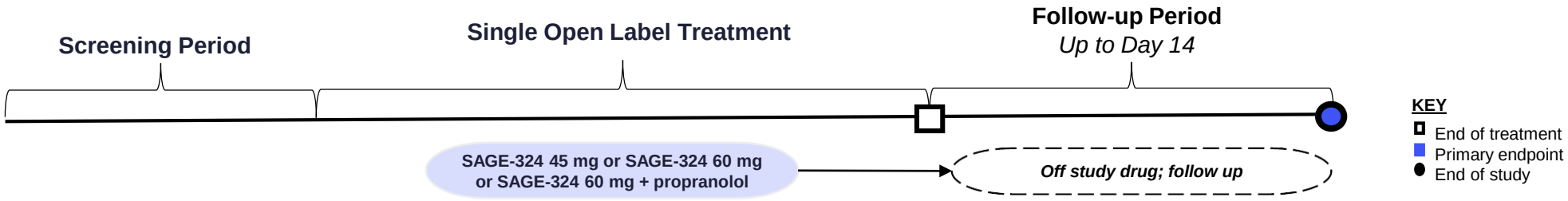
| | | | |
|---|---|---|---|
| **Status** | Complete | **Inclusion Criteria** | • Diagnosis of MDD with symptoms that have been present for at least a 4-week period<br>• MADRS total score ≥32 and HAM-D total score ≥22 at screening and Day 1 (prior to dosing) |
| **Indication** | MDD | | |
| **Phase** | Phase 3 | **Exclusion Criteria** | • Active psychosis<br>• Attempted suicide associated with the current episode of MDD<br>• Medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder |
| **Start/End Date*** <br>*topline data announced | Sep. 2018; Dec. 2019 | | |
| **Arms** | Double-blind, randomized: 1:1:1<br>• SAGE-217 20 mg, SAGE-217 30 mg, placebo | **Primary Endpoint** | • Change from baseline in HAM-D total score* |
| **Dosing Regimen** | 2-week, once-nightly | **Secondary Endpoints** | • Change from baseline in HAM-D, HAM-A*, MADRS, CGI-I, CGI-S**<br>• Incidence and severity of AE/SAE** |

Use of antidepressants, antianxiety or insomnia medications restricted during controlled follow-up period; however, these medications may be used during the naturalistic follow up period as indicated by clinical judgement of the Investigators

*During double-blind phase; **During double-blind and follow-up periods; NCT03672175. Available from: clinicaltrials.gov [accessed January 2020]

# **Completed** SAGE-324 Study

*Open-label essential tremor study (324-CLP-101E)*




**STUDY OVERVIEW**

| | | | |
|---|---|---|---|
| **Status** | Completed | **Inclusion Criteria** | • Diagnosis of ET consisting of<br>  • bilateral upper limb action tremor<br>  • at least 3 years duration<br>  • with or without tremor in other locations<br>  • absence of other neurological signs<br>• Combined TETRAS upper limb total score of ≥ 8 on the performance subscale part 4 |
| **Indication** | Essential Tremor (ET) | | |
| **Phase** | Phase 1 | **Exclusion Criteria** | • History or evidence of clinically relevant medical disorders (with exception of ET)<br>• Current or recent exposure to tremorgenic drugs or drug withdrawal state<br>• Previous surgery for the treatment of ET |
| **Start/End Date** | Aug. 2018 / Dec. 2019 | | |
| **Cohorts** | Open-label study:<br>• SAGE-324 45 mg<br>• SAGE-324 60 mg<br>• SAGE-324 60 mg + propranolol | **Primary Endpoint** | • Safety and tolerability as assessed by frequency and severity of AE/SAE |
| **Dosing Regimen** | Single dose | **Secondary Endpoints** | • PK profile of SAGE-324 |
| | | **Exploratory Endpoint** | • Change from baseline over time in TETRAS performance subscale and Kinesia™ accelerometer scores |

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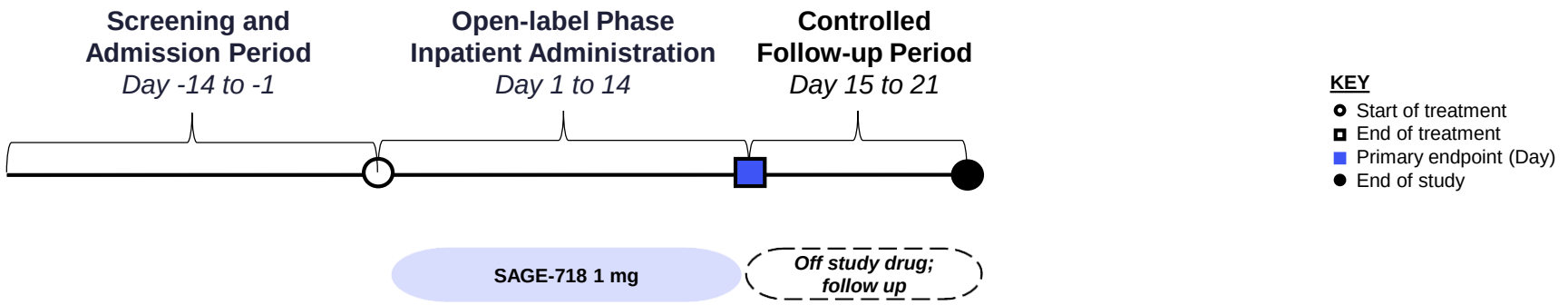
# **Completed** SAGE-718 Study

## *Open-label Cohort of Patients with Huntington's Disease (CLP-102 Part B)*




**STUDY OVERVIEW**

| | |
|---|---|
| **Status** | Completed |
| **Indication** | Huntington's Disease Cognitive Impairment |
| **Phase** | Phase 1 |
| **Start/End Date*** *topline data announced | Jan. 2019 / Dec. 2019 |
| **Arms** | Open-label SAGE-718 1 mg oral solution |
| **Dosing Regimen** | 2-week, once daily |

| | |
|---|---|
| **Inclusion Criteria** | • Positive for mutant *HTT* (documented CAG repeats ≥ 36 units)<br>• Total Functional Capacity (TFC) score > 6<br>• Score 28 or less on the MoCA at Screening |
| **Exclusion Criteria** | • Unstable co-morbid medical conditions |
| **Primary Endpoint** | • Incidence of adverse events and serious adverse events, and changes from baseline in vital signs, safety EEGs, ECGs, laboratory parameters, and Columbia-Suicide Severity Rating Scale (C-SSRS). |
| **Secondary and Other Endpoints** | • PK profile of SAGE-718 following administration of multiple doses of SAGE-718 oral solution<br>• Change from baseline on a computerized cognitive battery |

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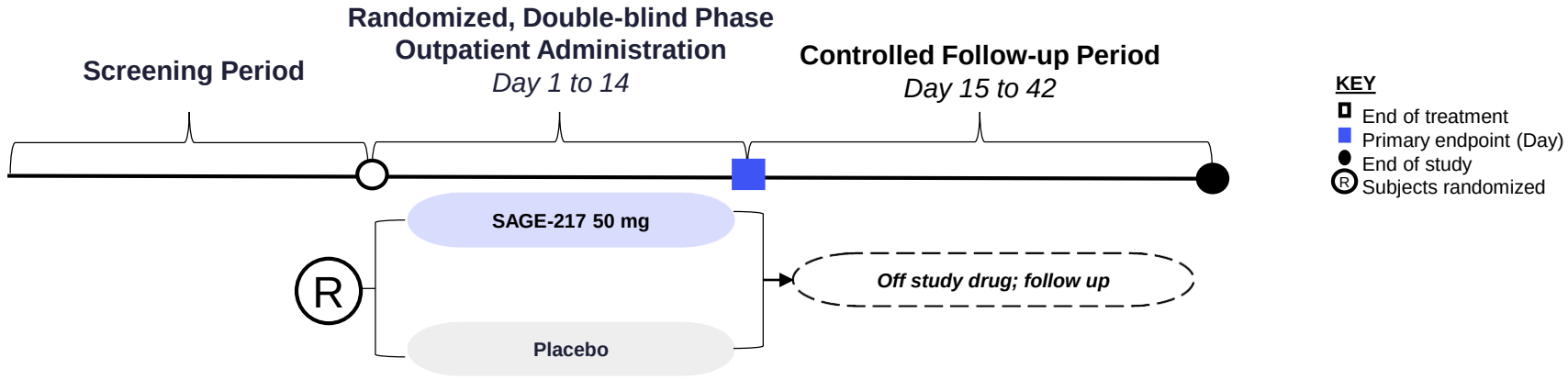
# Study Design:

## Planned / Ongoing Studies

# Zuranolone (SAGE-217) - 50 mg

## *New placebo-controlled **MDD** study - WATERFALL (MDD-301B)*



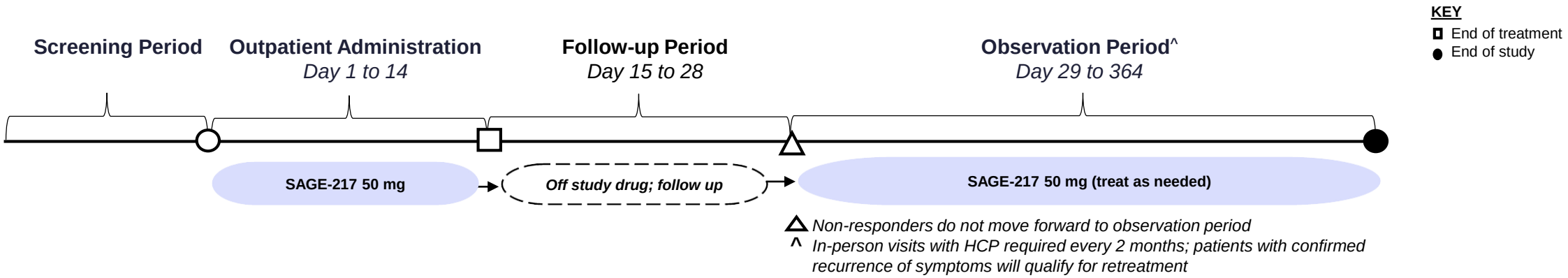

**STUDY OVERVIEW**

| | | | |
|---|---|---|---|
| **Status** | Planned 2020 Initiation | **Inclusion Criteria** | • Diagnosis of MDD with symptoms that have been present for at least a 4-week period<br>• HAM-D total score ≥24 at screening and Day 1 (prior to dosing) |
| **Indication** | MDD | | |
| **Phase** | Phase 3 | **Exclusion Criteria** | • Active psychosis<br>• Attempted suicide associated with the current episode of MDD<br>• Medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder |
| **Start/End Date** | May 2020 / TBA | | |
| **Arms** | Double-blind, randomized: 1:1<br>• SAGE-217 50 mg, placebo | **Primary Endpoint** | • Change from baseline in HAM-D total score at Day 15 |
| **Dosing Regimen** | 2-week, once-nightly | **Secondary Endpoints** | • Change from baseline in HAM-D, HAM-A, MADRS, CGI-I, CGI-S<br>• Incidence and severity of AE/SAE |

Use of antidepressants, antianxiety or insomnia medications restricted during controlled follow-up period

# Zuranolone (SAGE-217) - 50 mg

## *SHORELINE (**MDD**-303; 50 mg cohort)*




*50 mg will be examined in subjects having already received 30 mg, as well as enrollment of a new cohort of 50 mg only subjects*

**STUDY OVERVIEW**

| | | | |
|---|---|---|---|
| **Status** | Enrollment Complete (3Q 2019) | **Inclusion Criteria** | • MDD, as diagnosed by SCID-5-CT, with symptoms that have been present for at least a 4-week period<br>• Subject is in good physical health and has no clinically significant findings, as determined by the Investigator, on physical examination, 12-lead ECG, or clinical laboratory tests |
| **Data Timing** | TBA | **Exclusion Criteria** | • Attempted suicide associated with the current episode of MDD<br>• Medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder<br>• Subject has had vagus nerve stimulation, electroconvulsive therapy, or has taken ketamine (including esketamine) within the current major depressive episode |
| **Arms** | Non-randomized;<br>SAGE-217 50 mg | **Primary Endpoint** | • Safety and tolerability of the initial treatment and re-treatment as assessed by: incidence and severity of AEs; suicidal ideation and behavior using C-SSRS* |
| **Dosing Regimen** | 2-week, once-nightly | **Secondary Endpoints** | • Need for re-treatment, as assessed by time to first re-treatment, number of subjects achieving the requirements for re-treatment, number of re-treatment cycles for each subject*<br>• Response of initial treatment and/or retreatment, as assessed by:<br>  • Change from baseline in HAM-D, CGI-S*<br>  • Percent of subjects achieving: HAM-D response (≥50% reduction) and HAM-D remission (HAM-D total score ≤7) at the end of each 14-day treatment period*<br>  • Percent of subjects achieving CGI-I* |

*During double-blind and follow-up periods

NCT03864614. Available from: clinicaltrials.gov [accessed November 2019]





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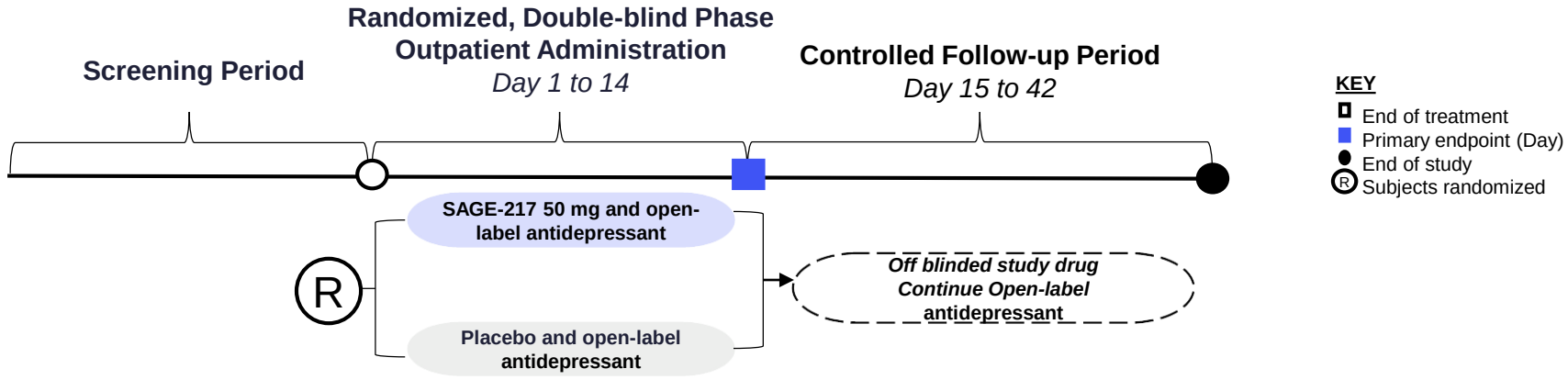
# Zuranolone (SAGE-217) - 50 mg

## *New active-controlled RRT when co-initiated with new ADT in **MDD** study – CORAL (MDD-305)*




**STUDY OVERVIEW**

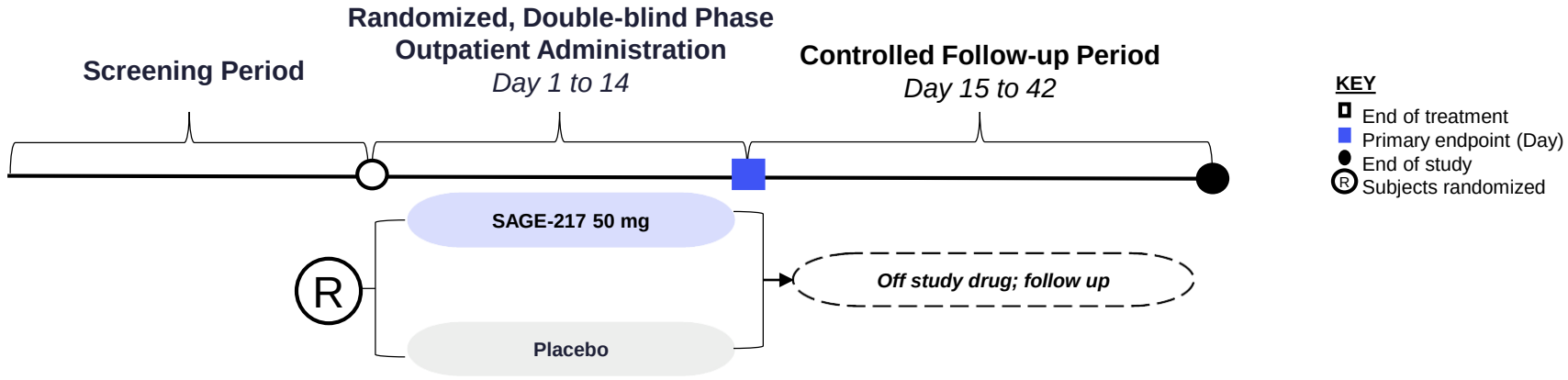
| | | | |
|---|---|---|---|
| **Status** | Planned 2020 Initiation | **Inclusion Criteria** | • Diagnosis of MDD with symptoms that have been present for at least a 4-week period<br>• HAM-D total score ≥24 at screening and Day 1 (prior to dosing) |
| **Indication** | MDD | | |
| **Phase** | Phase 3 | **Exclusion Criteria** | • Active psychosis<br>• Attempted suicide associated with the current episode of MDD<br>• Medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder |
| **Start/End Date** | TBA | | |
| **Arms** | Double-blind, randomized: 1:1<br>• SAGE-217 50 mg, placebo added to open-label antidepressant | **Primary Endpoint** | • Change from baseline in HAM-D total score at Day 15 |
| **Dosing Regimen** | 2-week, once-nightly | **Secondary Endpoints** | • Change from baseline in HAM-D, HAM-A, MADRS, CGI-I, CGI-S<br>• Incidence and severity of AE/SAE |

Use of antidepressants, antianxiety or insomnia medications restricted during controlled follow-up period

RRT = rapid response therapy

# Zuranolone (SAGE-217) - 50 mg

## *New placebo-controlled **PPD** study - SKYLARK (PPD-301)*



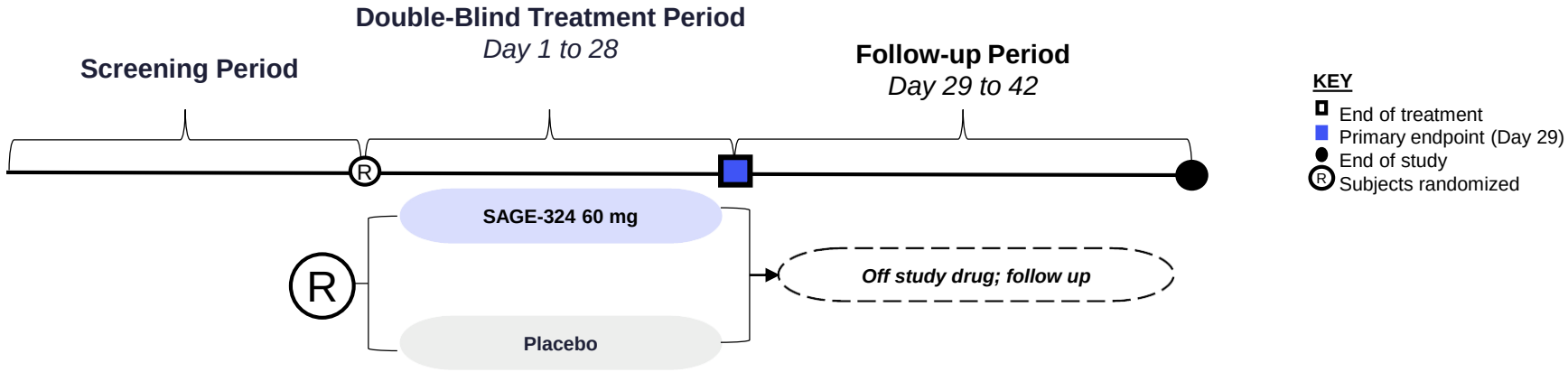

**STUDY OVERVIEW**

| | | | |
|---|---|---|---|
| **Status** | Planned 2020 Initiation | **Inclusion Criteria** | • Diagnosis of MDD with symptoms that have been present for at least a 4-week period<br>• HAM-D total score ≥26 at screening and Day 1 (prior to dosing) |
| **Indication** | PPD | | |
| **Phase** | Phase 3 | **Exclusion Criteria** | • Active psychosis<br>• Attempted suicide associated with the current episode of PPD<br>• Medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder |
| **Start/End Date** | Jun. 2020 / TBA | | |
| **Arms** | Double-blind, randomized: 1:1<br>• SAGE-217 50 mg, placebo | **Primary Endpoint** | • Change from baseline in HAM-D total score at Day 15 |
| **Dosing Regimen** | 2-week, once-nightly | **Secondary Endpoints** | • Change from baseline in HAM-D, HAM-A, MADRS, CGI-I, CGI-S<br>• Incidence and severity of AE/SAE |

Use of antidepressants, antianxiety or insomnia medications restricted during controlled follow-up period

# SAGE-324

## *Placebo-controlled **Essential Tremor** study - KINETIC (324-ETD-201)*




### STUDY OVERVIEW

| | |
|---|---|
| **Status** | Ongoing |
| **Indication** | Essential Tremor (ET) |
| **Phase** | Phase 2 |
| **Start/End Date** | TBA |
| **Arms** | Double-blind, randomized: 1:1<br>• SAGE-324 60 mg: placebo |
| **Dosing Regimen** | 28 days, once-daily |

**Inclusion Criteria**

- Diagnosis of ET consisting of
  - bilateral upper limb action tremor
  - at least 3 years duration
  - with or without tremor in other locations
  - absence of other neurological signs, sudden onset or evidence of stepwise deterioration of tremor
- Score of at least 1.5 for each TETRAS performance subscale part 4 items with total score for the dominant upper limb of at least 5.5

**Exclusion Criteria**

- Presence of known causes of enhanced physiological tremor
- Recent exposure to tremorgenic drugs or presence of alcohol withdrawal state
- Direct or indirect injury or trauma to the nervous system within 3 months before the onset of tremor
- Previous procedure for the treatment of ET, deep brain stimulation, brain lesioning, or magnetic resonance guided procedure

**Primary Endpoint**

- Change from baseline in TETRAS performance subscale part 4 upper limb tremor score on Day 29

**Secondary Endpoints**

- Change from baseline in TETRAS performance subscale part 4 upper limb tremor score at all other timepoints
- Change from baseline in Kinesia ONE accelerometer scores

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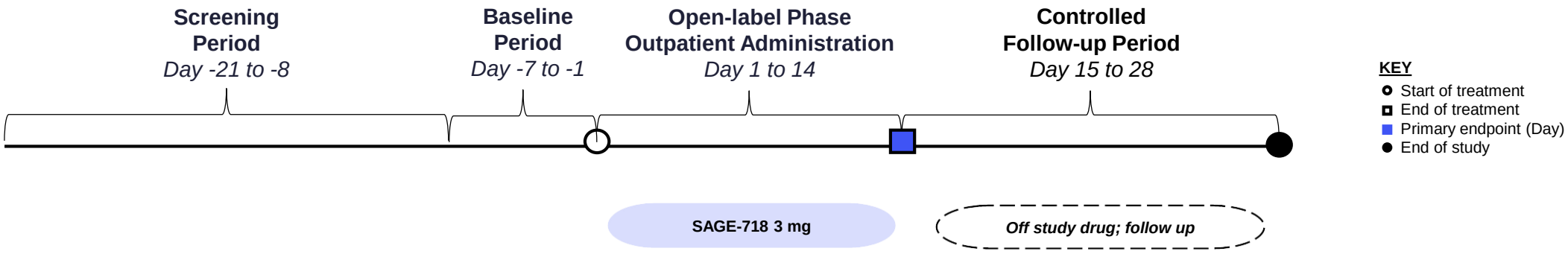
# SAGE-718

## *New Open-label **Parkinson's Mild Cognitive Impairment** Study – PARADIGM (CNP-201)*




**STUDY OVERVIEW**

| | | | |
|---|---|---|---|
| **Status** | Start-up | **Inclusion Criteria** | • Diagnosis of Parkinson's Disease Mild Cognitive Impairment<br>• Score 20 to 25 (inclusive) on the MoCA at Screening |
| **Indication** | PD-MCI | | |
| **Phase** | Phase 2 | **Exclusion Criteria** | • Diagnosis of dementia of any etiology<br>• Experiencing fluctuations in motor and/or non-motor symptoms of Parkinson's disease |
| **Start/End Date** | TBA | | |
| **Arms** | Open-label SAGE-718 3 mg oral tablet | **Primary Endpoint** | • Incidence of treatment-emergent adverse events (TEAEs) |
| **Dosing Regimen** | 2-week, once daily | **Secondary and Other Endpoints** | • Change from baseline in vital signs, clinical laboratory analytes, electrocardiograms, and responses on the Columbia–Suicide Severity Rating Scale (C-SSRS)<br>• Change from baseline on comprehensive neurocognitive and neuropsychiatric batteries |

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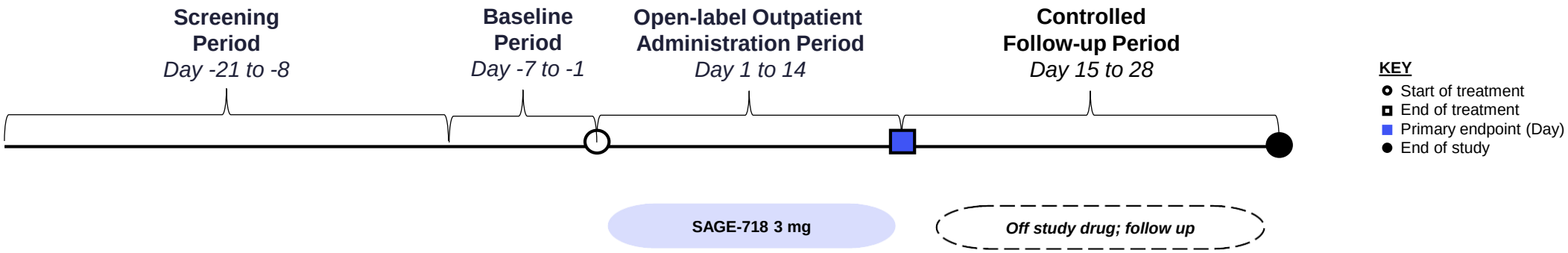
# SAGE-718

## *New Open-label **Alzheimer's Mild Cognitive Impairment and Mild Dementia** Study – LUMINARY (CNA-201)*




**STUDY OVERVIEW**

| | | | |
|---|---|---|---|
| **Status** | Start-up | **Inclusion Criteria** | • Diagnosis of MCI or mild dementia due to Alzheimer's Disease<br>• Score 15 to 24 (inclusive) on the MoCA at Screening |
| **Indication** | AD-MCI and Mild AD Dementia | | |
| **Phase** | Phase 2 | **Exclusion Criteria** | • Have any medical or neurological condition (other than AD) that might be contributing to the participant's cognitive impairment or history of cognitive decline |
| **Start/End Date** | TBA | | |
| **Arms** | Open-label SAGE-718 3 mg oral tablet | **Primary Endpoint** | • Incidence of treatment-emergent adverse events (TEAEs) |
| **Dosing Regimen** | 2-week, once daily | **Secondary and Other Endpoints** | • Change from baseline in vital signs, clinical laboratory analytes, electrocardiograms, and responses on the Columbia–Suicide Severity Rating Scale (C-SSRS)<br>• Change from baseline on comprehensive neurocognitive and neuropsychiatric batteries |

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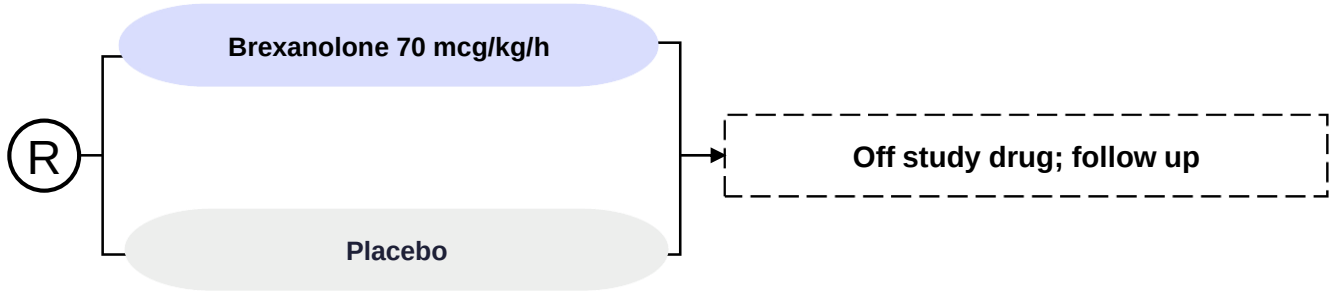
# Clinical Study Design – ARDS Due to COVID-19


**Key**
- ▲ End of treatment
- ● End of study
- Ⓡ Subjects randomized




**STUDY OVERVIEW**

| | | | |
|---|---|---|---|
| **Indication** | Acute Respiratory Distress Syndrome (ARDS) due to COVID-19 | **Inclusion Criteria** | • Positive for SARS-CoV-2<br>• ARDS<br>• Intubated and receiving mechanical ventilation for <48 hours at screening |
| **Phase** | Phase 3 | **Primary Endpoint** | • Percentage of subjects alive and free of respiratory failure at Day 28 |
| **Arms** | Double-blind, randomized:1:1<br>• Brexanolone 70 mcg/kg/h<br>• Placebo | **Secondary Endpoints** | • Treatment-emergent adverse events<br>• All-cause mortality through Day 28 |
| **Dosing Regimen** | 60 Hour Continuous IV Infusion | **Additional Endpoints** | • Respiratory parameters<br>• Change in cytokines and inflammatory markers<br>• Changes in anesthetic dose |

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