



# Investor Presentation

August 2020

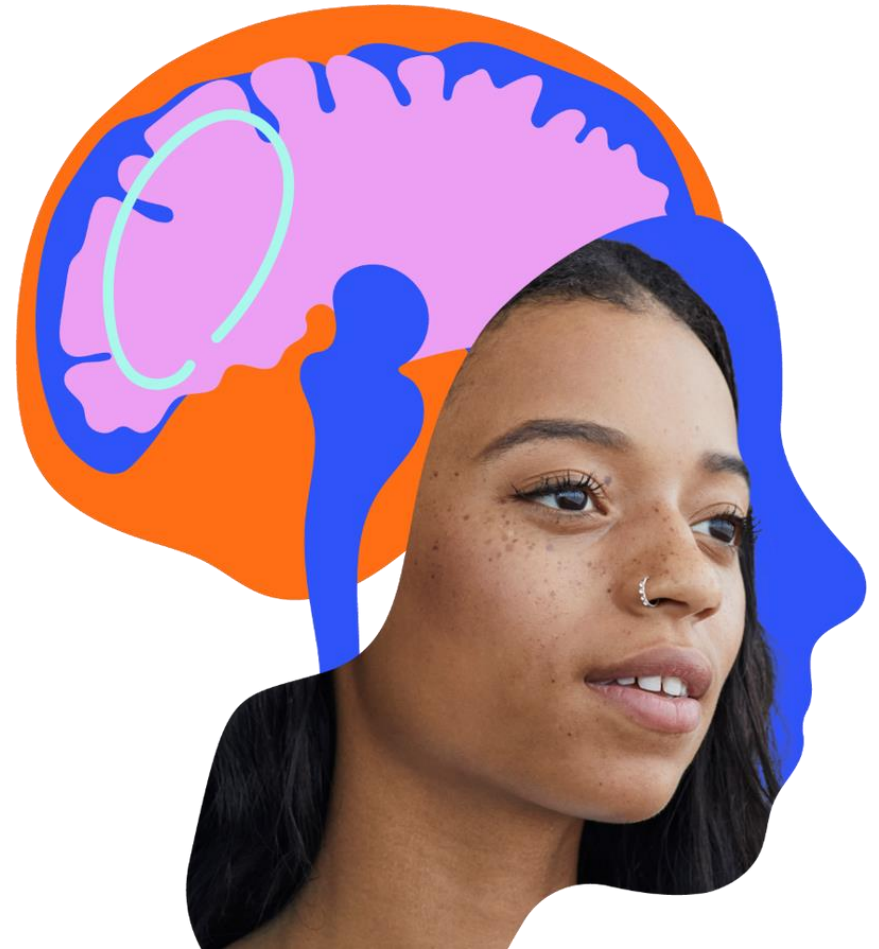


# Safe Harbor Statement

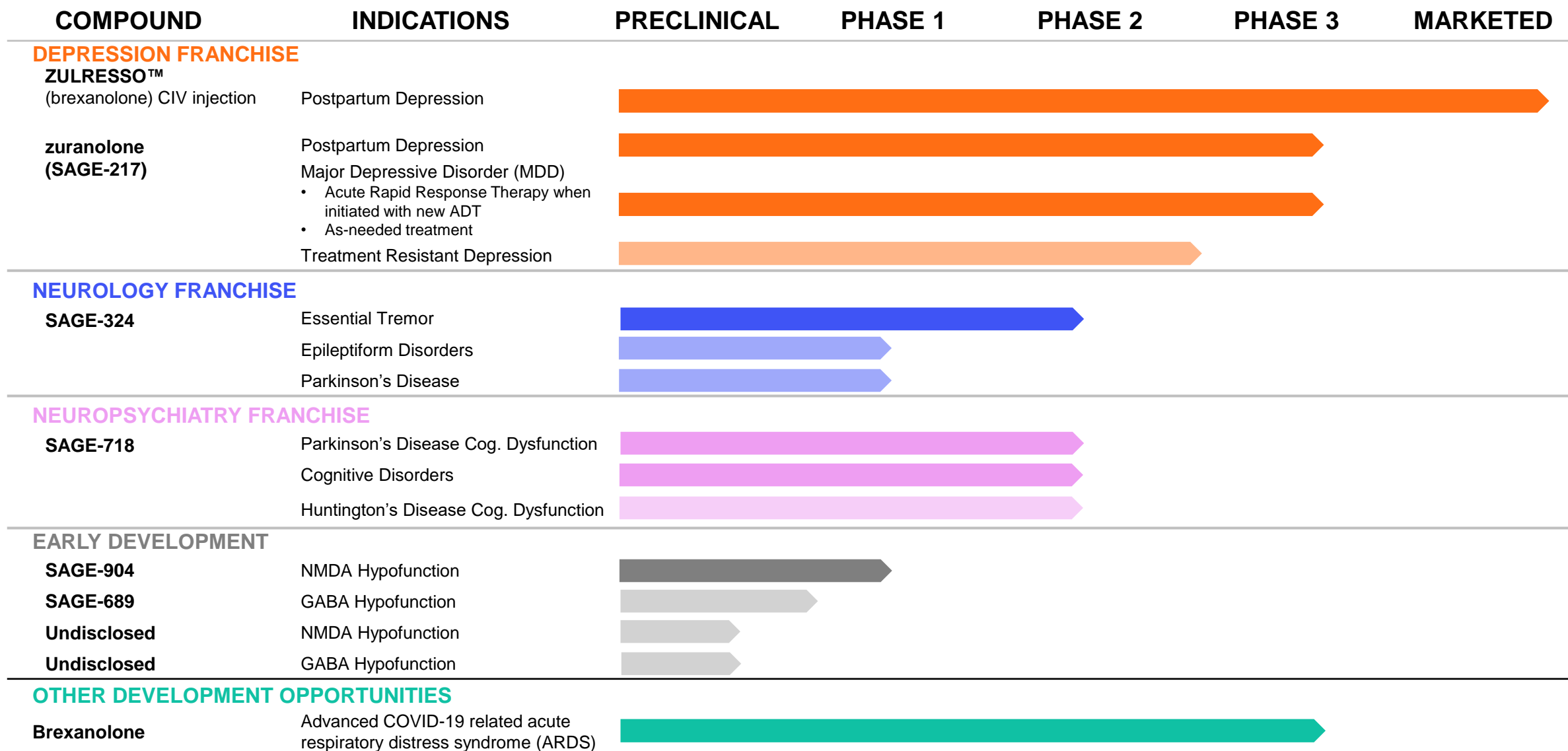
- The slides presented today and the accompanying oral presentations contain forward-looking statements, which may be identified by the use of words such as “may,” “might,” “will,” “should,” “expect,” “plan,” “anticipate,” “believe,” “estimate,” “project,” “intend,” “future,” “opportunity,” “goal,” “potential,” 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 and the expected continuing impact of the COVID-19 pandemic on ZULRESSO revenues; our clinical development plans and expected timelines; the potential regulatory pathways for our product candidates; 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 the sale 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, 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 or conduct in 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 or planning to study 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.

# 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 **9** indications
  - In-house library of **>6K** proprietary compounds
  - **\$759M** cash-on-hand as of June 30, 2020



# A Leading Brain Health Portfolio



# Depression Franchise

# Psychiatry as Medicine

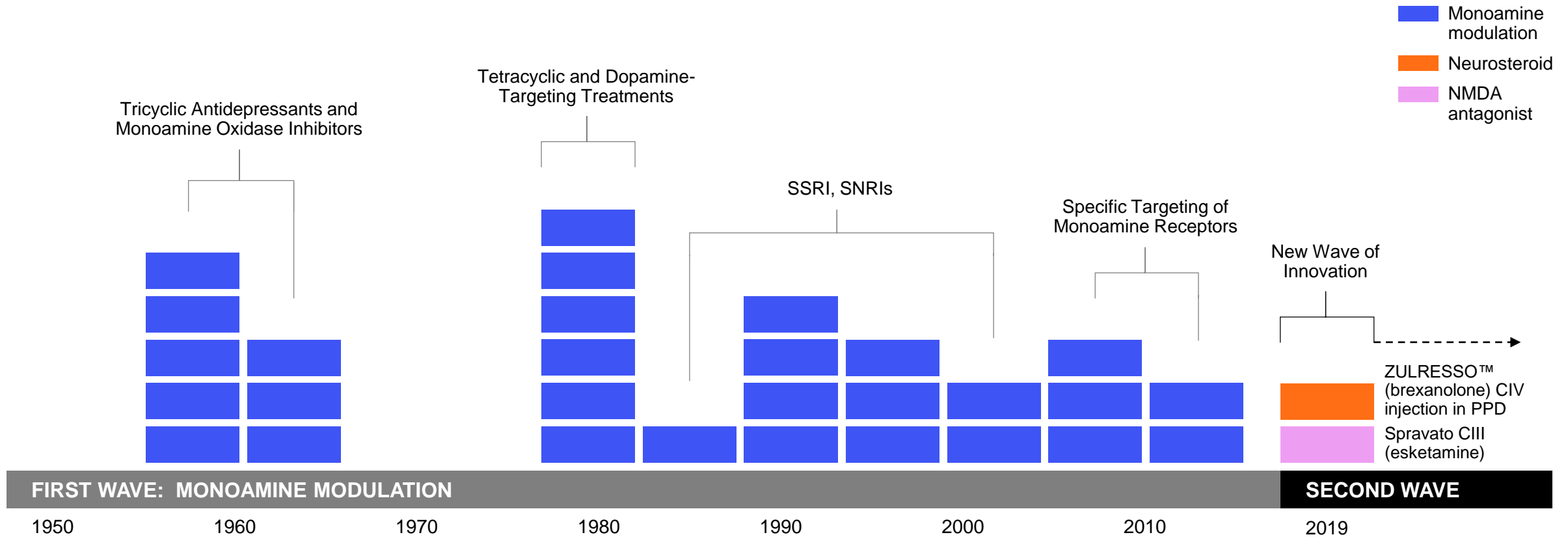
Our goal is to develop medicines to treat depression with potentially unique efficacy and tolerability profiles that:

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

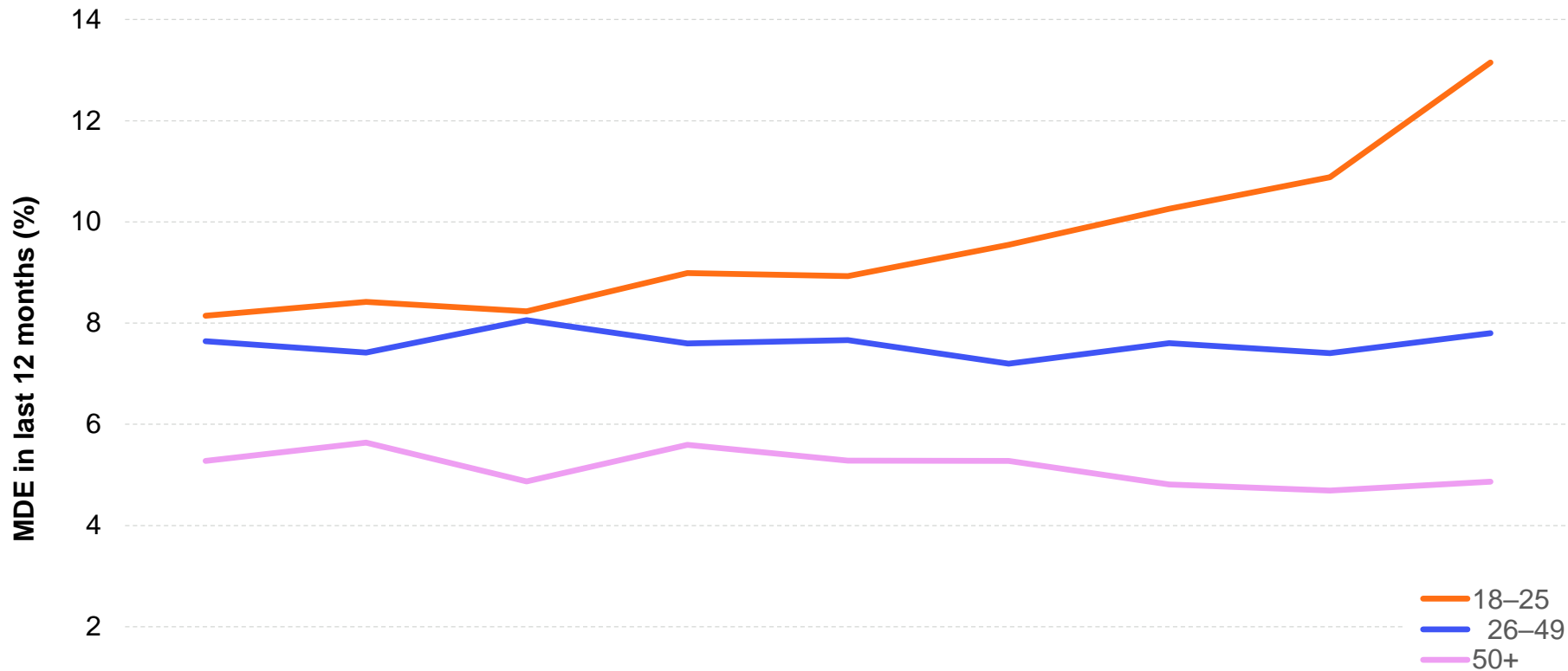


# Sage Leading Second Wave of Neuropsych Innovation

## *First new MOA in 60 years*



# 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



# Zuranolone's (SAGE-217) Landscape Program

*Potential to reshape the depression landscape*

STUDY	<u>PPD-201</u>	<u>SKYLARK</u> (PPD-301)	<u>MDD-201</u>	<u>MOUNTAIN</u> (MDD-301)	<u>WATERFALL</u> (MDD-301B)	<u>REDWOOD</u> (MDD-302)	<u>SHORELINE</u> (MDD-303)	<u>RAINFOREST</u> (MDD-304)	<u>CORAL</u> (MDD-305)
Indication	PPD	PPD	MDD	MDD	MDD	MDD	MDD	Co-morbid MDD and Insomnia	MDD
Phase	Pivotal Ph. 2	Pivotal Ph. 3	Pivotal Ph. 2	Pivotal Ph. 3	Pivotal Ph. 3	Pivotal Ph. 3	Pivotal Ph. 3	Pivotal Ph. 3	Pivotal Ph. 3
Objective	Efficacy in the treatment of PPD compared to placebo	Efficacy in the treatment of PPD compared to placebo	Efficacy in the treatment of MDD compared to placebo	Efficacy in the treatment of MDD compared to placebo	Efficacy in the treatment of MDD compared to placebo	Efficacy of a fixed, repeated treatment regimen in the prevention of relapse	Safety, tolerability of as-needed repeat treatment over a 1-year period	Efficacy in the treatment of sleep efficiency	Efficacy, compared to placebo, in the treatment of MDD when co-initiated with open-label ADT
Status / Anticipated Timing	Complete	Ongoing; topline data in 2021	Complete	Complete	Ongoing; topline data in 1H 2021	Enrollment paused; future re-evaluation planned	Enrollment for 30 mg cohort complete, with topline data by year-end 2020; ongoing enrollment for 50 mg cohort with topline data in 2021	Enrollment paused; future re-evaluation planned	Planned 2020 initiation; topline data in 2021

# Development Plan for Zuranolone Creates Flexibility to Pursue an Efficient and Expedited Pathway to Filing

## Potential for 3 distinct indications

### ORAL POSTPARTUM DEPRESSION (PPD) THERAPY

**SKYLARK (PPD-301):** Placebo-controlled trial evaluating a two-week course of zuranolone 50 mg in women with PPD, with additional *short-term* follow-up

+

Previously completed studies; no additional long-term follow-up expected to be required

### ACCUTE RAPID RESPONSE (RRT) IN MAJOR DEPRESSIVE DISORDER (MDD) WHEN COINITIATED WITH NEW ADT

**MDD-305:** Placebo-controlled trial evaluating a two-week course of zuranolone 50 mg, when co-initiated with an open-label antidepressant, in patients with MDD, with additional *short-term* follow-up

+

Previously completed studies; no additional long-term follow-up expected to be required

### AS NEEDED THERAPY IN PATIENTS WITH MDD

**WATERFALL (MDD-301B):** Placebo-controlled trial evaluating a two-week course of zuranolone 50 mg in patients with MDD, with additional *short-term* follow-up

+

Previously completed acute treatment studies and long-term safety data, including data from REDWOOD (MDD-302)

Distinct indications enable Sage to efficiently pursue NDA filing for zuranolone and, if successful, bring this treatment to patients quickly

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.

# 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



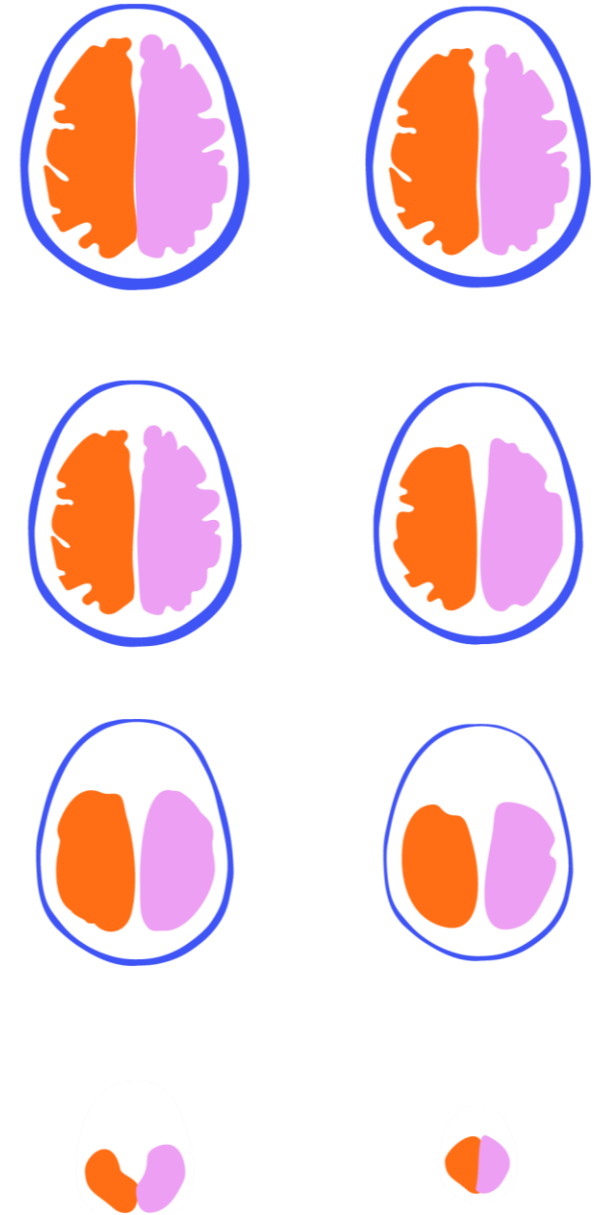
**Please see Boxed Warning and Important Safety Information**

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

# Neurology Franchise

# Next-generation Asset Positioned for Neurological Conditions

- **SAGE-324**
  - Novel next-generation positive allosteric modulator (PAM) of GABA<sub>A</sub> 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



# SAGE-324 in Essential Tremor

## *Initiated 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<sup>1</sup>
- Approximately 50% of diagnosed patients receive pharmacotherapy for ET<sup>2</sup>

### **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 – 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<sup>3</sup>

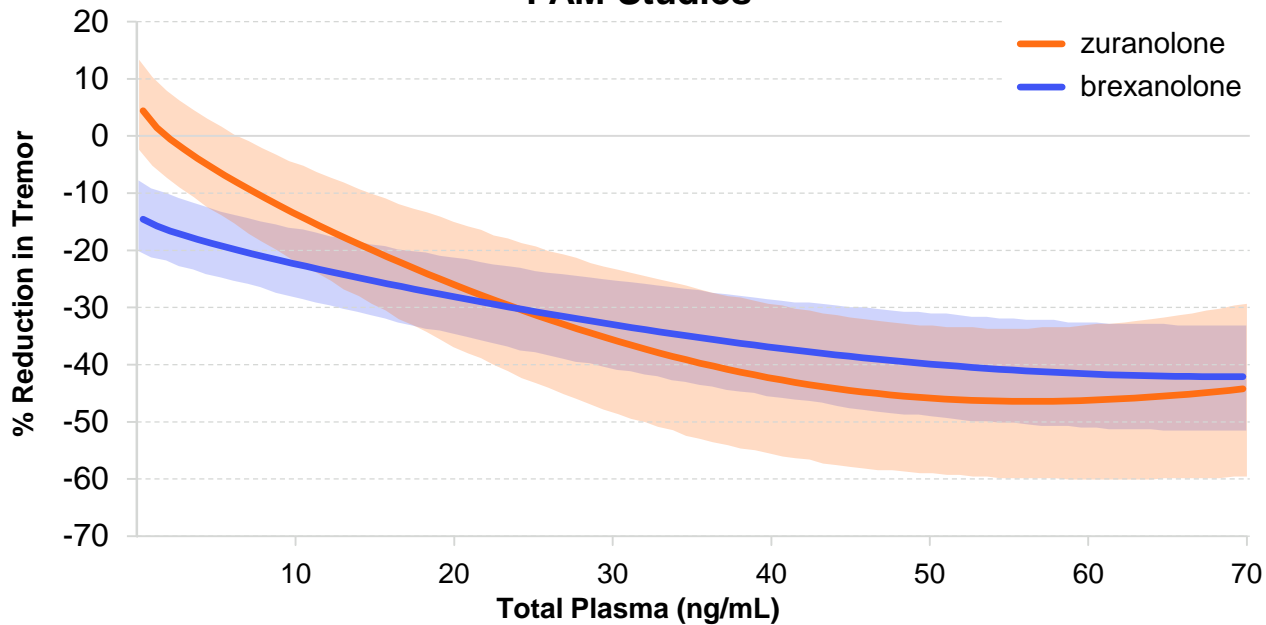
Medications are generally  
effective in about

**50%**  
of patients who seek treatment<sup>4</sup>

# Initiated Phase 2 Study in Essential Tremor

*Phase 1 open-label study evaluating the safety and pharmacokinetics of SAGE-324 in patients with ET*

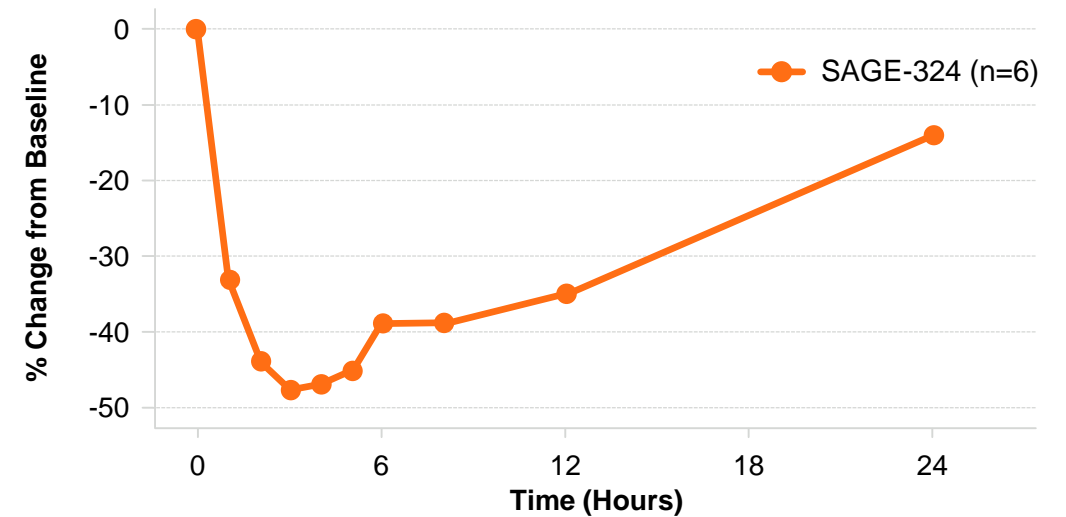
**Reduction in Tremor Observed in Other Sage GABA PAM Studies**



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

**SAGE-324 EFFECT OBSERVED AFTER A SINGLE DOSE**

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



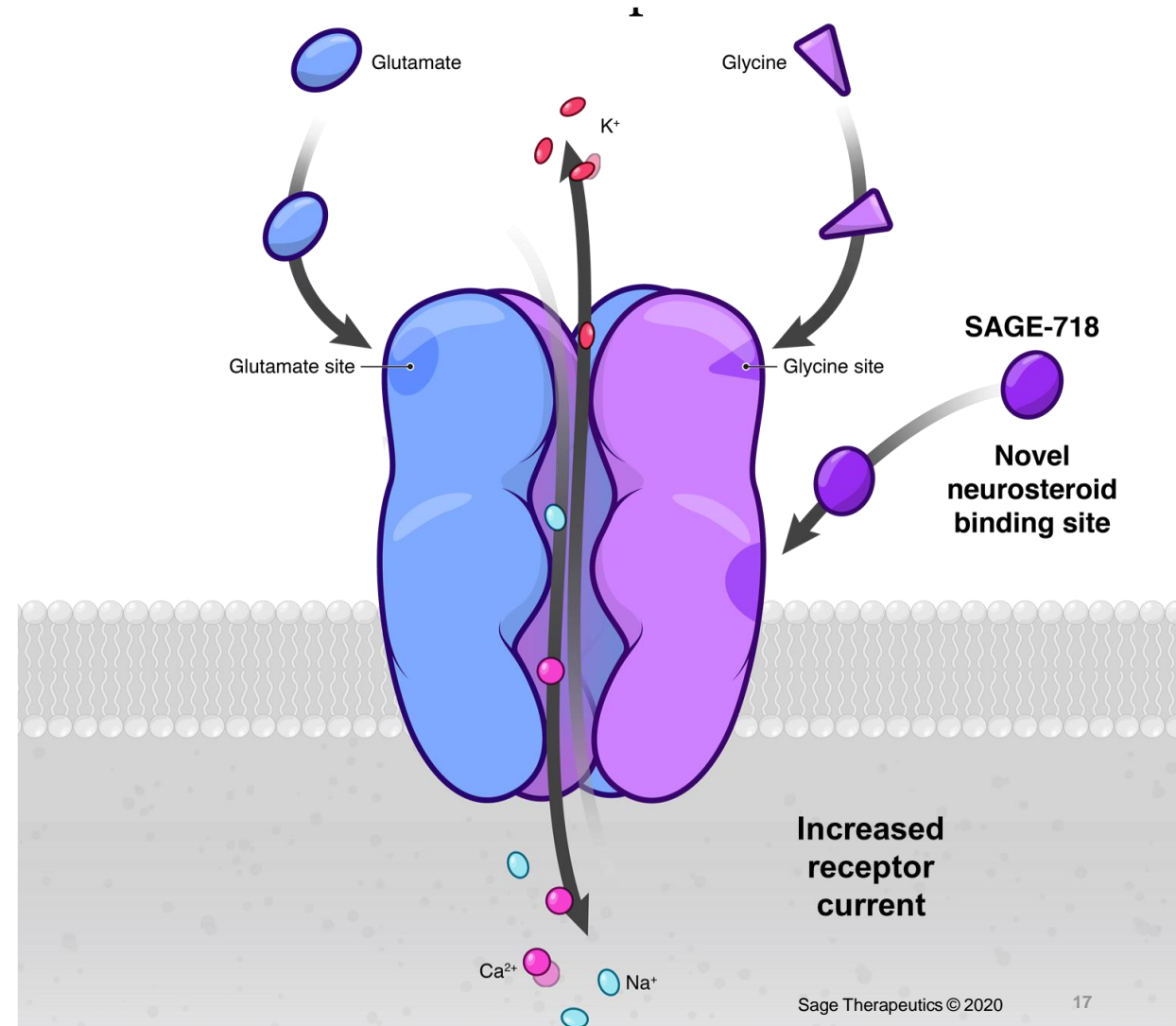
# Neuropsychiatry Franchise



# Sage's First-in-Class NMDA PAM

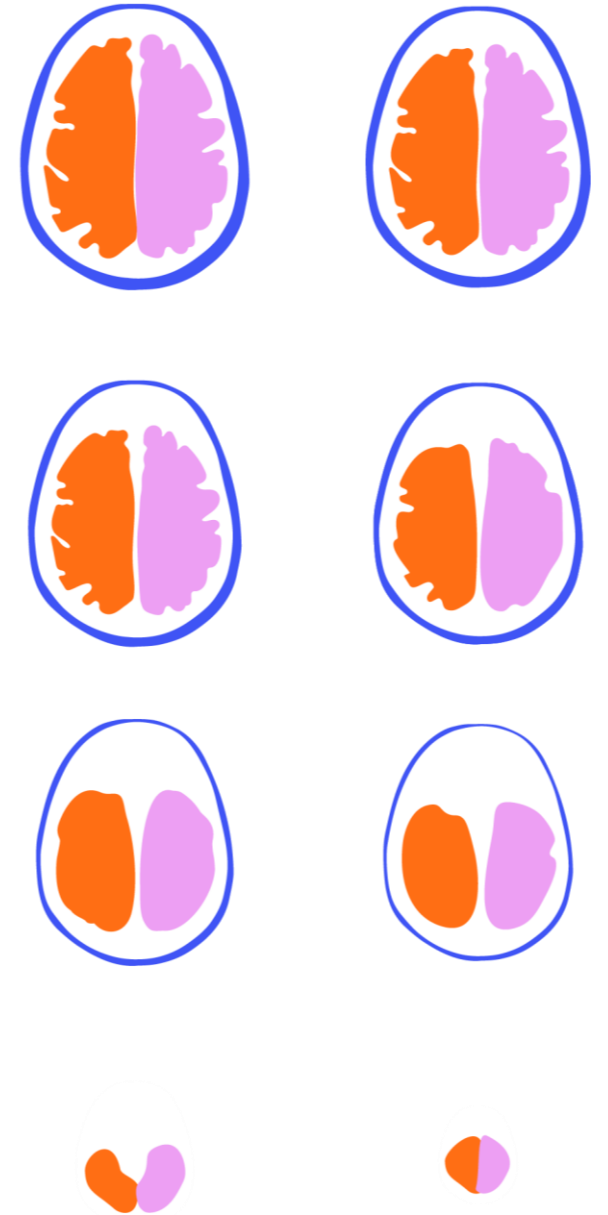
- NMDA receptors are thought to play a key role in a host of cognitive and behavioral processes
- Sage identified an endogenous modulator of the NMDA receptor (24S-hydroxycholesterol)
  - Yields potential biomarkers for activity and drug development
- Sage has built a library of thousands of novel NMDA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



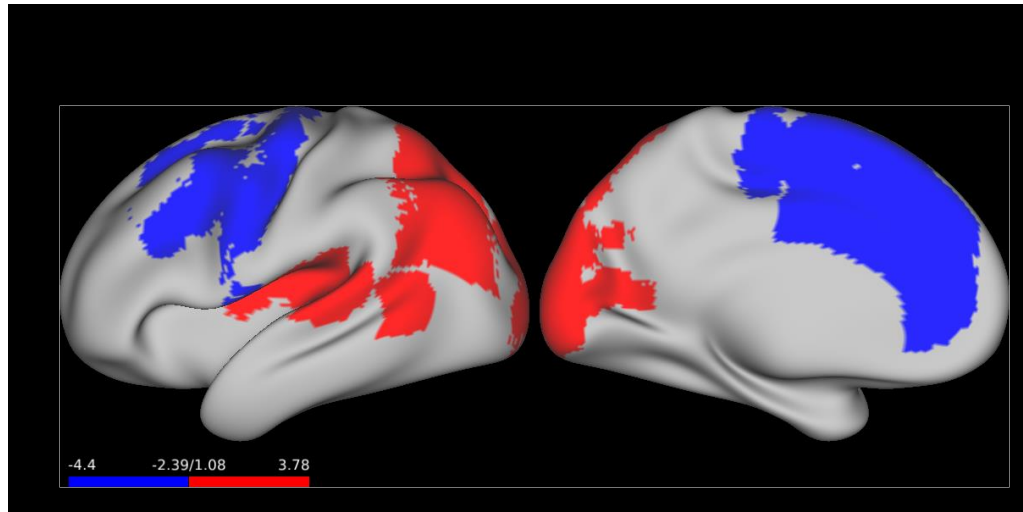
# SAGE-718 Data Suggest Potentially Transformational Activity in the Brain

- 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



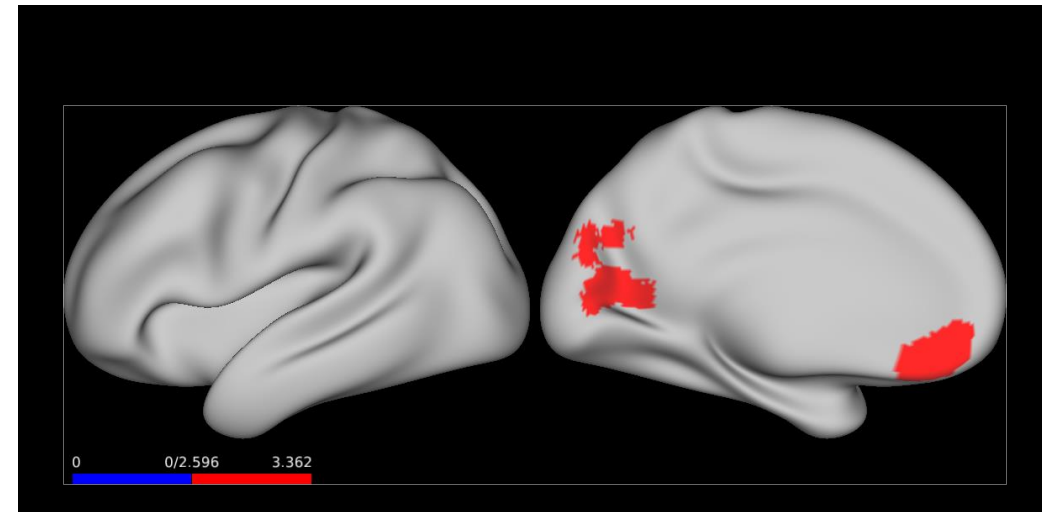
# SAGE-718 Attenuated Effects of Ketamine on Brain Circuits, in Phase 1 Study

## KETAMINE



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

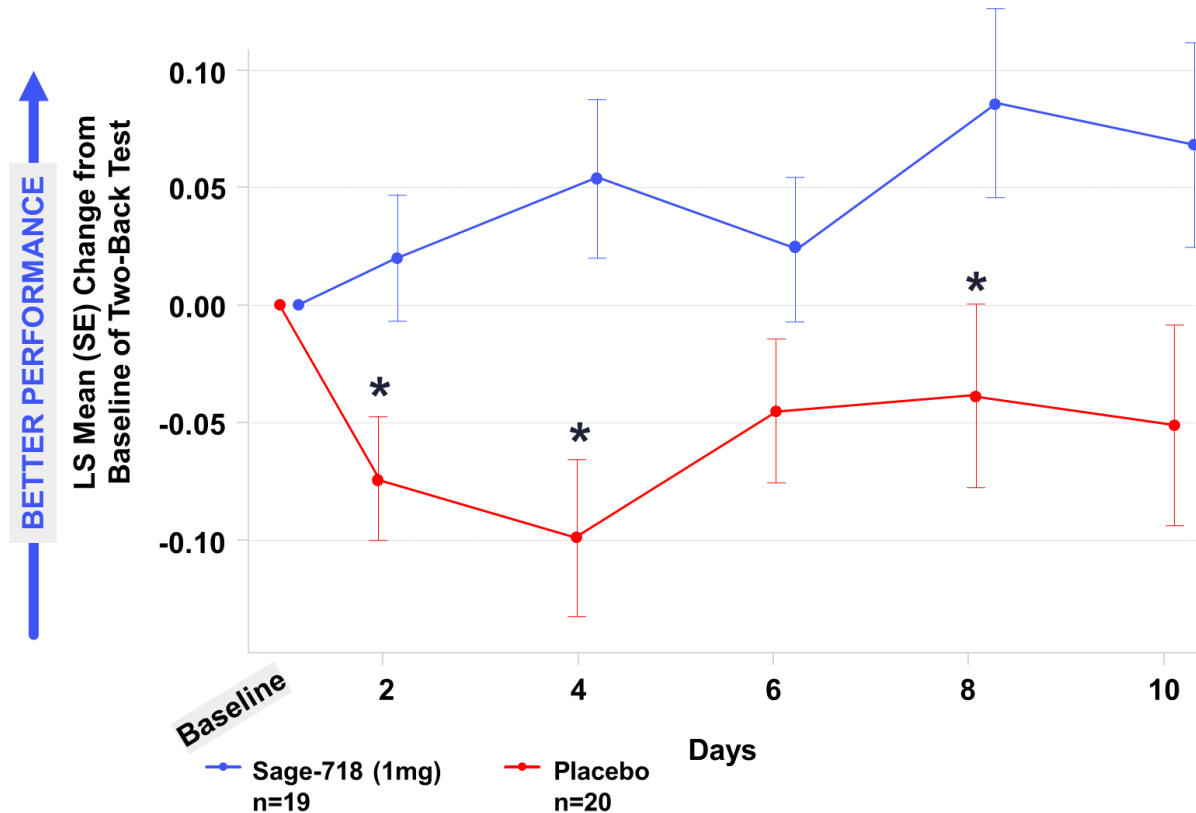
## SAGE-718 + KETAMINE



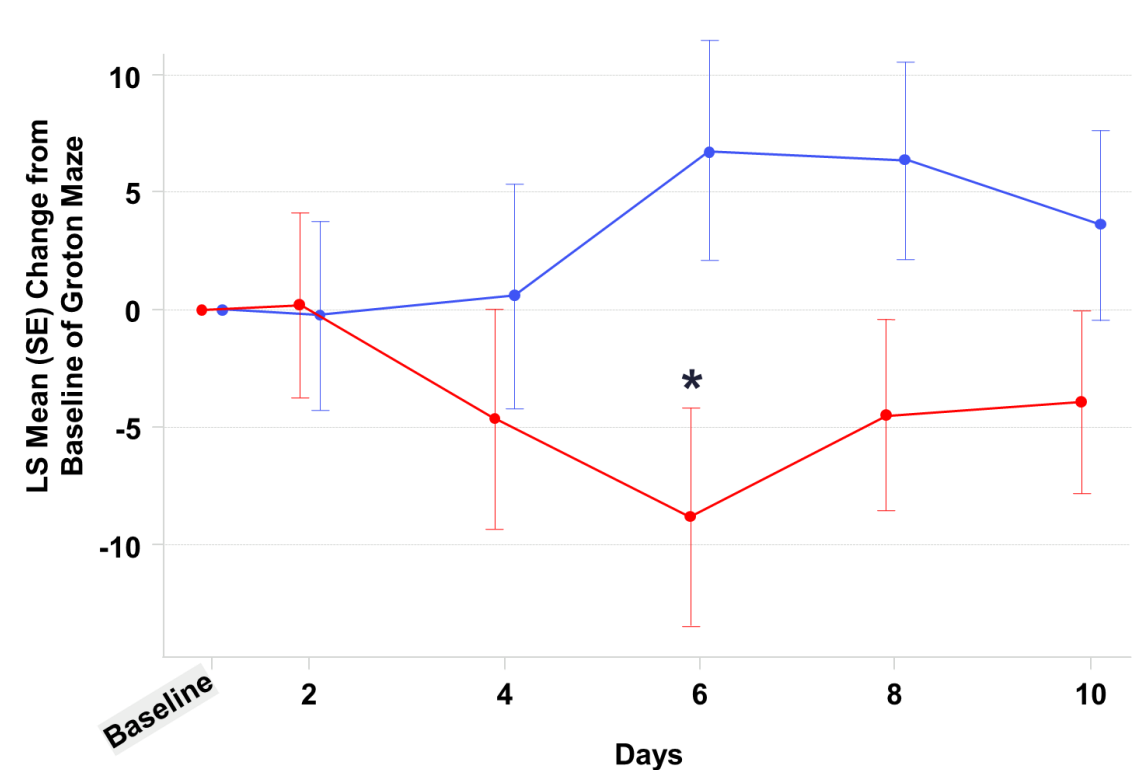
SAGE-718 blunted ketamine's induced increases and decreases in BOLD-MRI

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

WORKING MEMORY



PROBLEM SOLVING

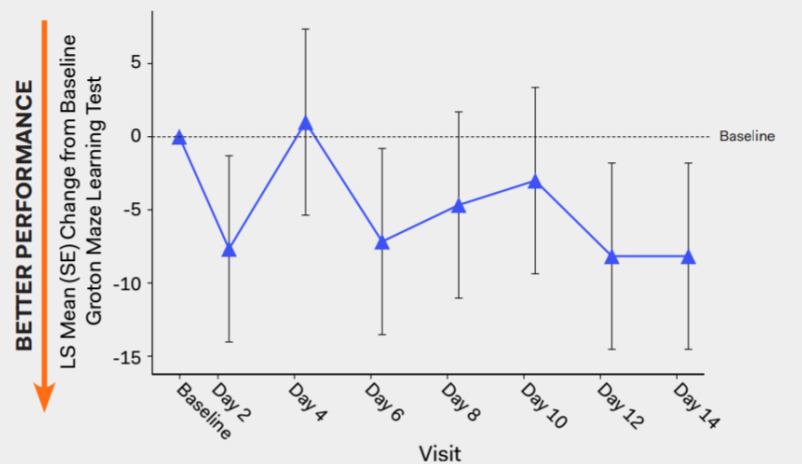


\* $p < 0.05$ . A MMRM model was applied with change from baseline in each cognitive assessment test score as the response variable and treatment, visit, visit-by-treatment interaction as fixed effect, baseline as covariate, and measurements within the same subject as repeated measure. Unstructured covariance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

# In Phase 1 HD Cohort, SAGE-718 Demonstrated Consistent Activity on Executive Functioning

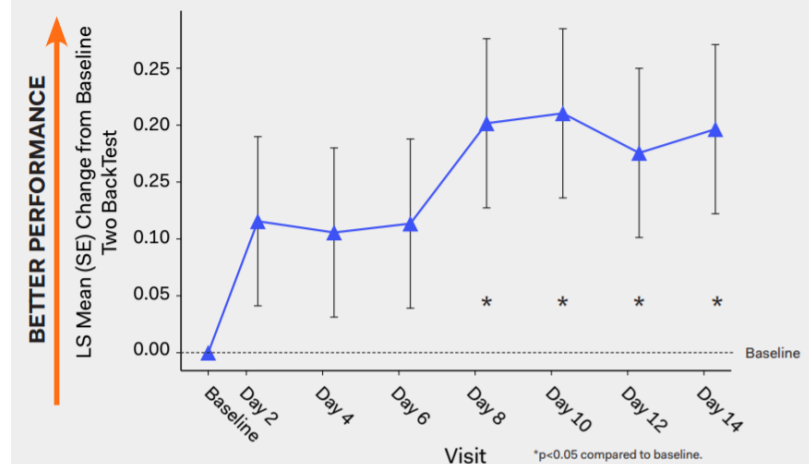
*Improvement on two tests of executive functioning, not driven by performance on other domains*

## GROTON MAZE TEST (Executive Function)



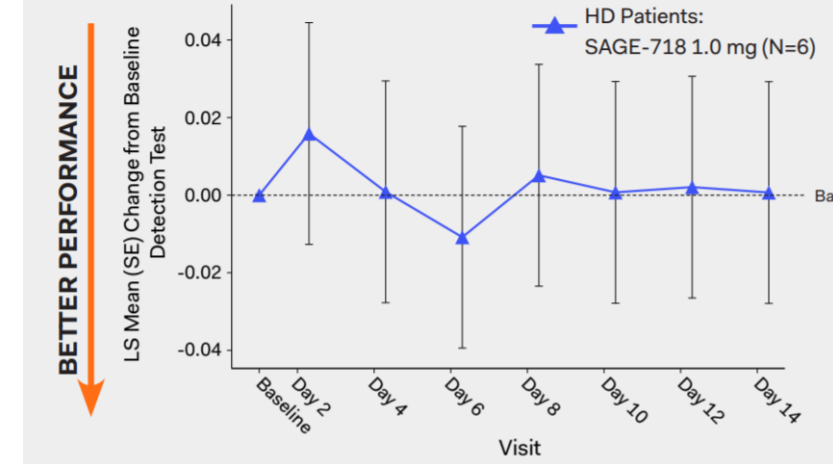
HD subjects demonstrated numerical improvement on the Groton Maze Test at all post-baseline visits, with the exception of Day 4.

## TWO-BACK TEST (Complex Working Memory and Executive Function)



HD subjects demonstrated numerical improvement on the Two-Back test at all post-baseline visits, and demonstrated statistically-significant ( $p < 0.05$ ) improvement compared to baseline on Days 8, 10, 12 and 14.

## DETECTION TEST (Psychomotor Speed)



Improvement on tests of executive functioning was not driven by performance on simpler tests of cognitive performance, as demonstrated by consistent performance on the detection test, a test of psychomotor speed.

# Second Quarter 2020 Financial Results

*Strong financial position with \$759M in cash*

Item	Q2 '20	Q2 '19
Revenue:	\$1.1M	\$0.9M
• <i>Zulresso</i>	• 1.1M	• 0.5M
• <i>Collaboration</i>	• -	• 0.4M
R&D Expense	\$73.3M	\$89.1M
SG&A Expense	\$38.2M	\$88.2M
Restructuring Expense	\$28.4M	-
COGS	\$0.1M	-
Total Operating Costs and Expenses	\$140.1M	\$177.3M
Net Loss	(\$136.3M)	(\$168.2M)
Cash and Marketable Securities	\$759M	\$1.2B

- 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.

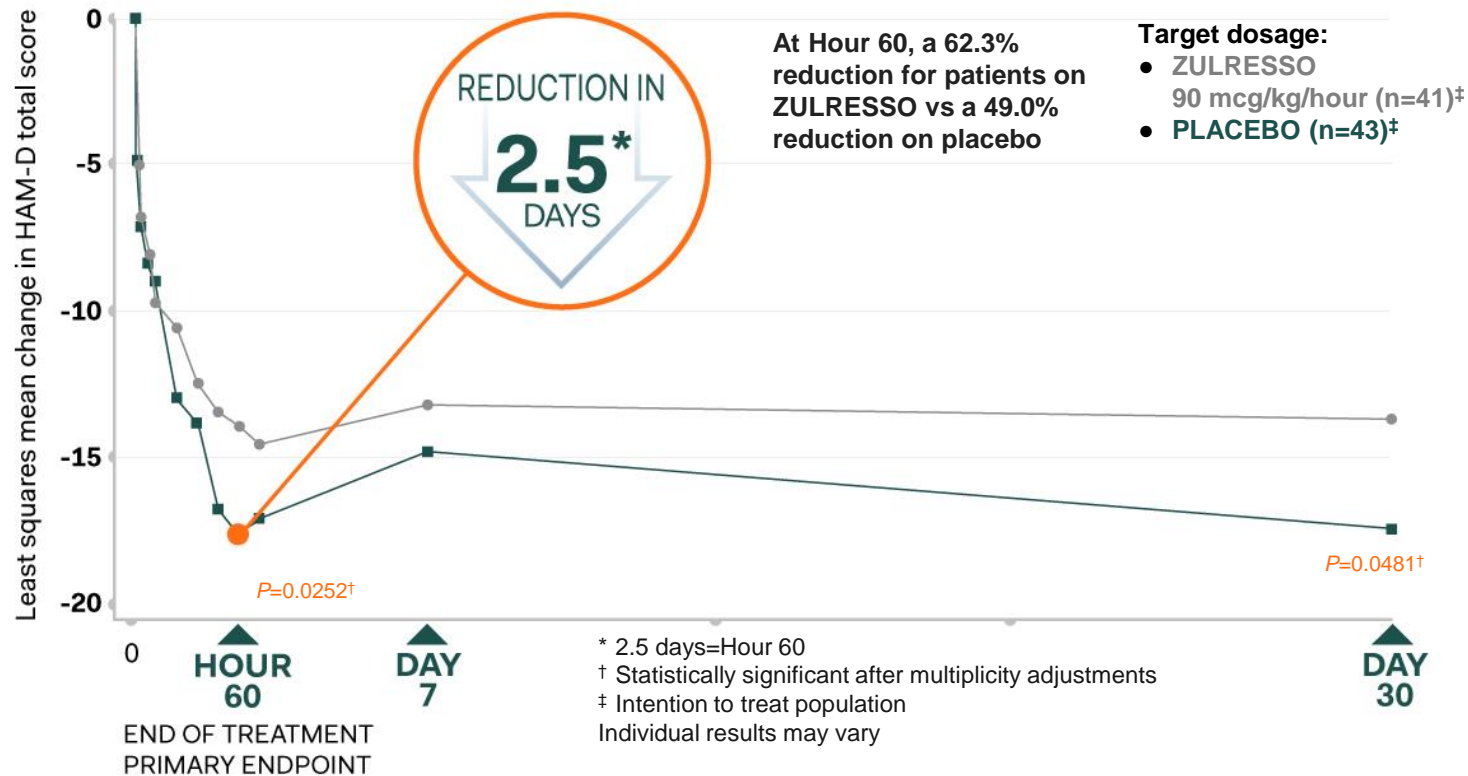
# Appendix



# 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)<sup>i,ii</sup>



## Durable therapeutic effect

A prespecified secondary efficacy endpoint was the mean change from baseline in HAM-D total score at Day 30<sup>i</sup>

In Study 1, significantly greater symptom reduction vs placebo was observed at Day 30<sup>i,ii</sup>

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<sup>iii</sup>

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





# 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)

# 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.**

# 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



**\$90M**

Upfront payment

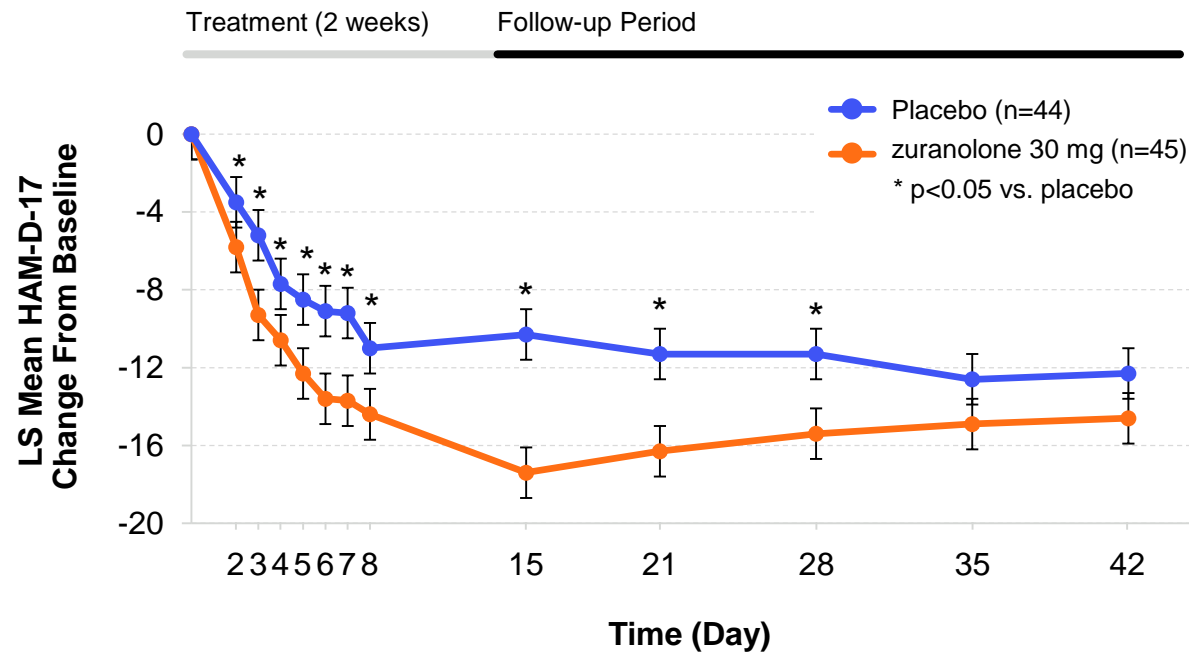
**\$485M**

Potential development & commercial milestones

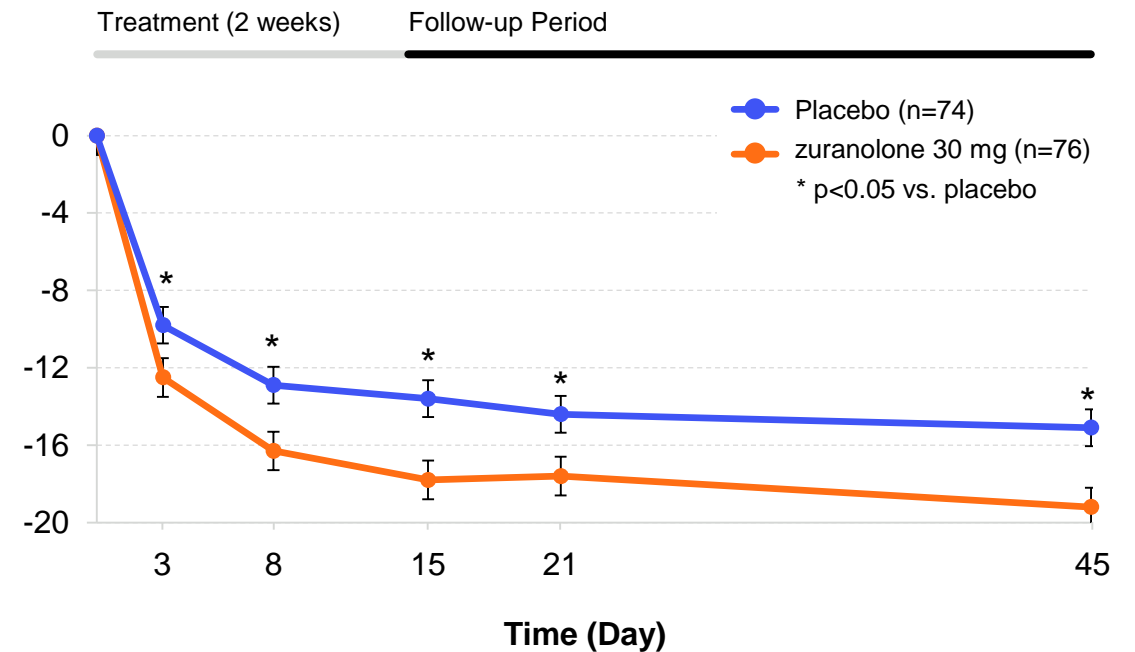
# MDD-201 & ROBIN Studies

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

## MDD-201



## ROBIN (PPD-201)



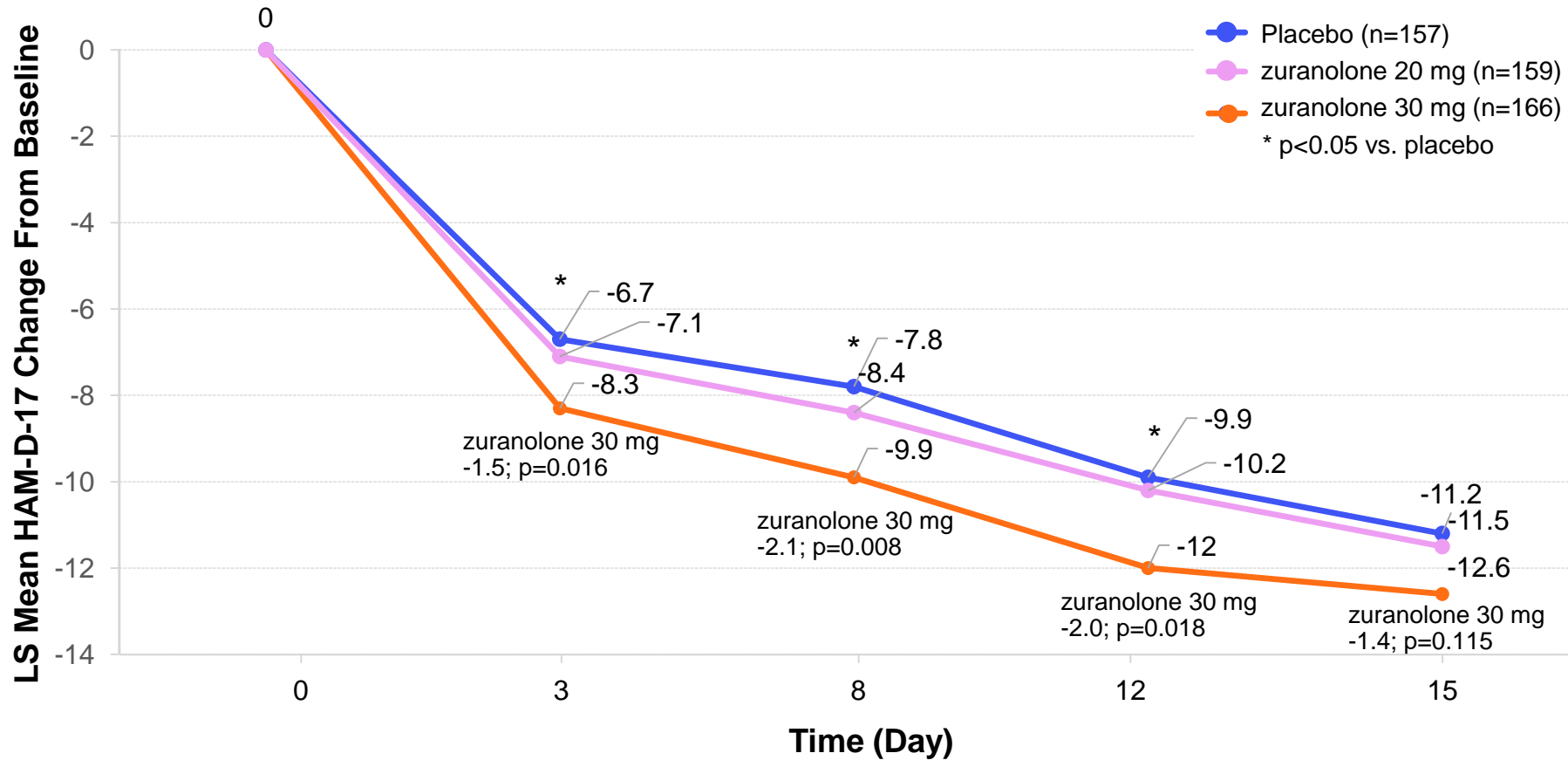
Zuranolone was generally well-tolerated in both studies

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

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

# 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 ( $\geq 5\%$ ) included headache, dizziness, somnolence, fatigue, diarrhea, sedation and nausea

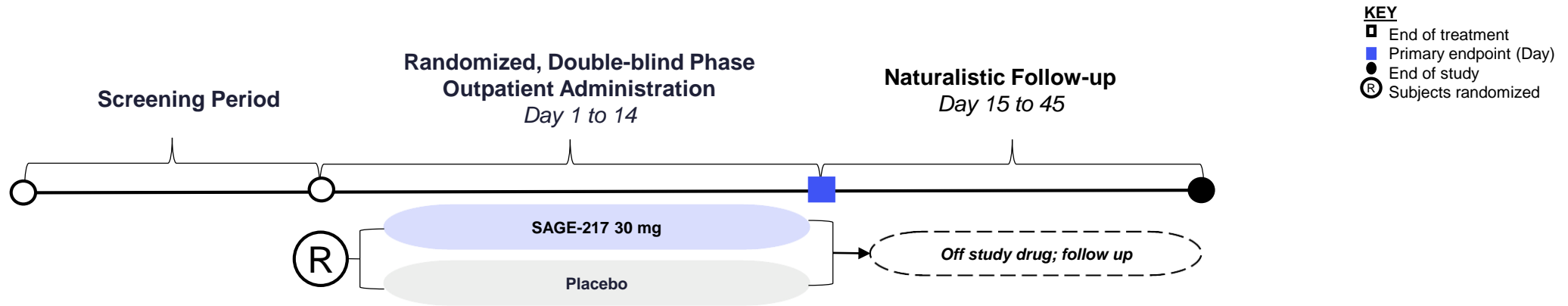
Rapid onset of effect for zuranolone 30 mg was seen beginning at Day 3 with maintenance of effect through Day 15; statistical separation from placebo observed Days 3 – 12

# Study Design:

Completed Studies

# Completed SAGE-217 Studies

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

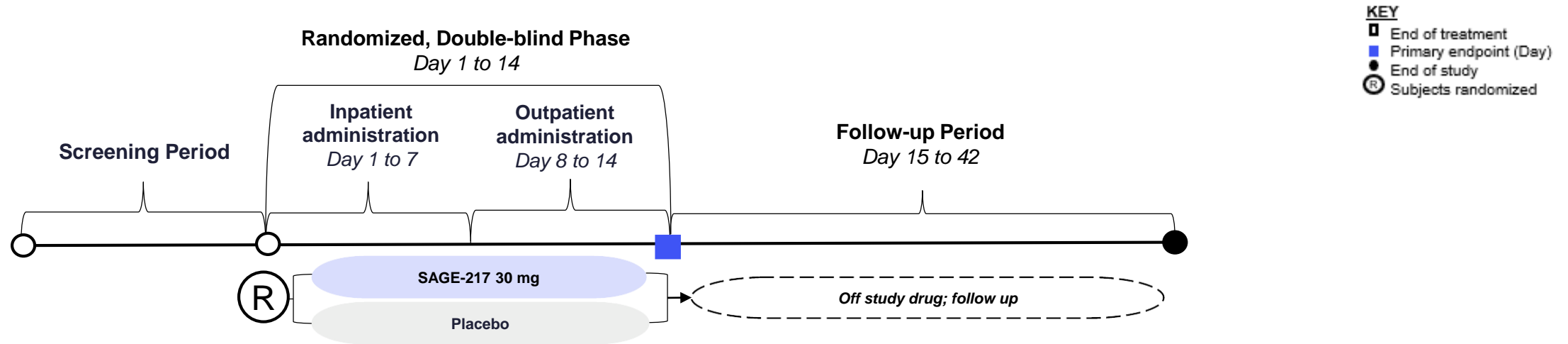


### STUDY OVERVIEW

<b>Arms</b>	Randomization: 1:1 • SAGE-217 30 mg • Placebo	<b>Key Inclusion Criteria</b>	<ul style="list-style-type: none"> <li>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</li> <li>Subject is ≤ six months postpartum</li> <li>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)</li> </ul>	<b>Primary Endpoint</b>	<ul style="list-style-type: none"> <li>Change from baseline in HAM-D total score*</li> </ul>
<b>Dosing Regimen</b>	2-week, once-nightly	<b>Key Exclusion Criteria</b>	<ul style="list-style-type: none"> <li>Active psychosis</li> <li>Attempted suicide associated with current episode of PPD (Note, suicidal ideation is not an exclusion; other protocol-defined inclusion/exclusion criteria may apply)</li> <li>Medical history of seizures, bipolar disorder, schizophrenia, and/or schizoaffective disorder</li> </ul>	<b>Secondary Endpoints</b>	<ul style="list-style-type: none"> <li>Safety and tolerability compared with placebo as assessed by: <ul style="list-style-type: none"> <li>Incidence of AEs, vital signs, clinical laboratory evaluations, ECG parameters**</li> <li>C-SSRS**</li> </ul> </li> </ul>

# Completed SAGE-217 Studies

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



### STUDY OVERVIEW

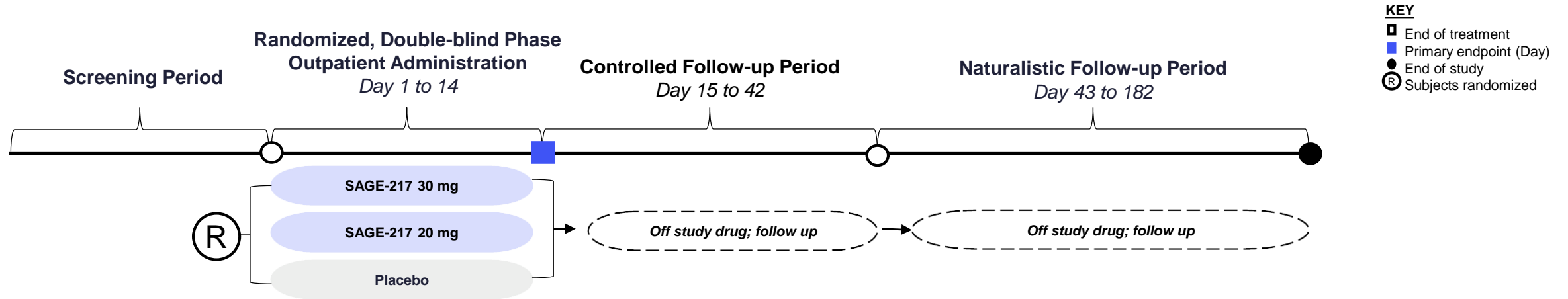
<b>Arms</b>	Randomization: 1:1 • SAGE-217 30 mg • Placebo	<b>Inclusion Criteria</b>	• Diagnosis of MDD with symptoms that have been present for at least a 4-week period	<b>Primary Endpoint</b>	• Change from baseline in HAM-D*
<b>Dosing Regimen</b>	2-week, once-nightly	<b>Exclusion Criteria</b>	• History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





# Completed SAGE-217 Studies

## Phase 3 MOUNTAIN (MDD-301)



### STUDY OVERVIEW

<b>Status</b>	Complete	<b>Inclusion Criteria</b>	<ul style="list-style-type: none"> <li>• Diagnosis of MDD with symptoms that have been present for at least a 4-week period</li> <li>• MADRS total score <math>\geq 32</math> and HAM-D total score <math>\geq 22</math> at screening and Day 1 (prior to dosing)</li> </ul>
<b>Indication</b>	MDD	<b>Exclusion Criteria</b>	<ul style="list-style-type: none"> <li>• Active psychosis</li> <li>• Attempted suicide associated with the current episode of MDD</li> <li>• Medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder</li> </ul>
<b>Phase</b>	Phase 3	<b>Primary Endpoint</b>	<ul style="list-style-type: none"> <li>• Change from baseline in HAM-D total score*</li> </ul>
<b>Start/End Date*</b> <small>*topline data announced</small>	Sep. 2018; Dec. 2019	<b>Secondary Endpoints</b>	<ul style="list-style-type: none"> <li>• Change from baseline in HAM-D, HAM-A*, MADRS, CGI-I, CGI-S**</li> <li>• Incidence and severity of AE/SAE**</li> </ul>
<b>Arms</b>	Double-blind, randomized: 1:1:1 • SAGE-217 20 mg, SAGE-217 30 mg, placebo		
<b>Dosing Regimen</b>	2-week, once-nightly		

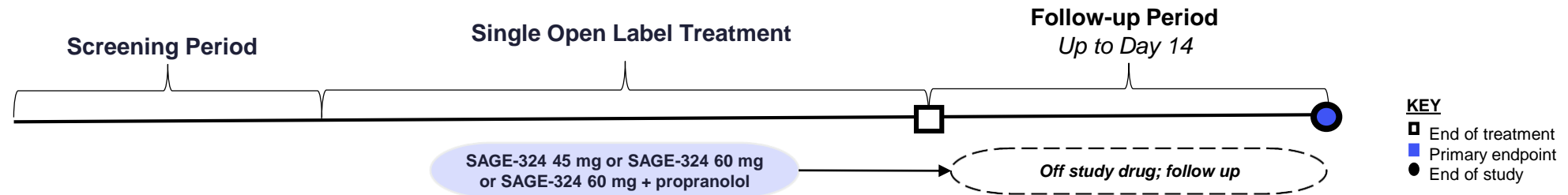


Use of antidepressants, anti-anxiety or insomnia medications restricted during controlled follow-up period; however, these medications may be used during the naturalistic follow up period as indicated by clinical judgement of the Investigators

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

# Completed SAGE-324 Study

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

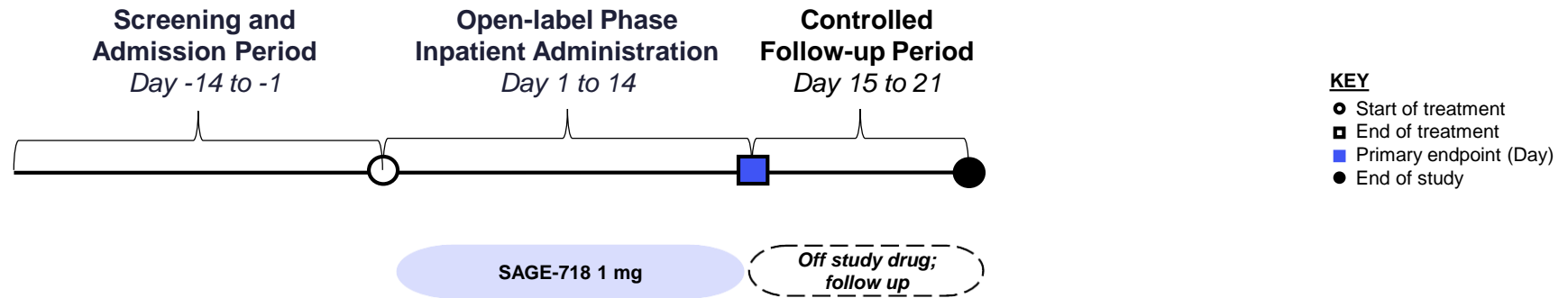


### STUDY OVERVIEW

<b>Status</b>	Completed		
<b>Indication</b>	Essential Tremor (ET)	<b>Inclusion Criteria</b>	<ul style="list-style-type: none"> <li>• Diagnosis of ET consisting of             <ul style="list-style-type: none"> <li>• bilateral upper limb action tremor</li> <li>• at least 3 years duration</li> <li>• with or without tremor in other locations</li> <li>• absence of other neurological signs</li> </ul> </li> <li>• Combined TETRAS upper limb total score of <math>\geq 8</math> on the performance subscale part 4</li> </ul>
<b>Phase</b>	Phase 1	<b>Exclusion Criteria</b>	<ul style="list-style-type: none"> <li>• History or evidence of clinically relevant medical disorders (with exception of ET)</li> <li>• Current or recent exposure to tremorgenic drugs or drug withdrawal state</li> <li>• Previous surgery for the treatment of ET</li> </ul>
<b>Start/End Date</b>	Aug. 2018 / Dec. 2019	<b>Primary Endpoint</b>	<ul style="list-style-type: none"> <li>• Safety and tolerability as assessed by frequency and severity of AE/SAE</li> </ul>
<b>Cohorts</b>	Open-label study: <ul style="list-style-type: none"> <li>• SAGE-324 45 mg</li> <li>• SAGE-324 60 mg</li> <li>• SAGE-324 60 mg + propranolol</li> </ul>	<b>Secondary Endpoints</b>	<ul style="list-style-type: none"> <li>• PK profile of SAGE-324</li> </ul>
<b>Dosing Regimen</b>	Single dose	<b>Exploratory Endpoint</b>	<ul style="list-style-type: none"> <li>• Change from baseline over time in TETRAS performance subscale and Kinesia™ accelerometer scores</li> </ul>

# Completed SAGE-718 Study

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



### STUDY OVERVIEW

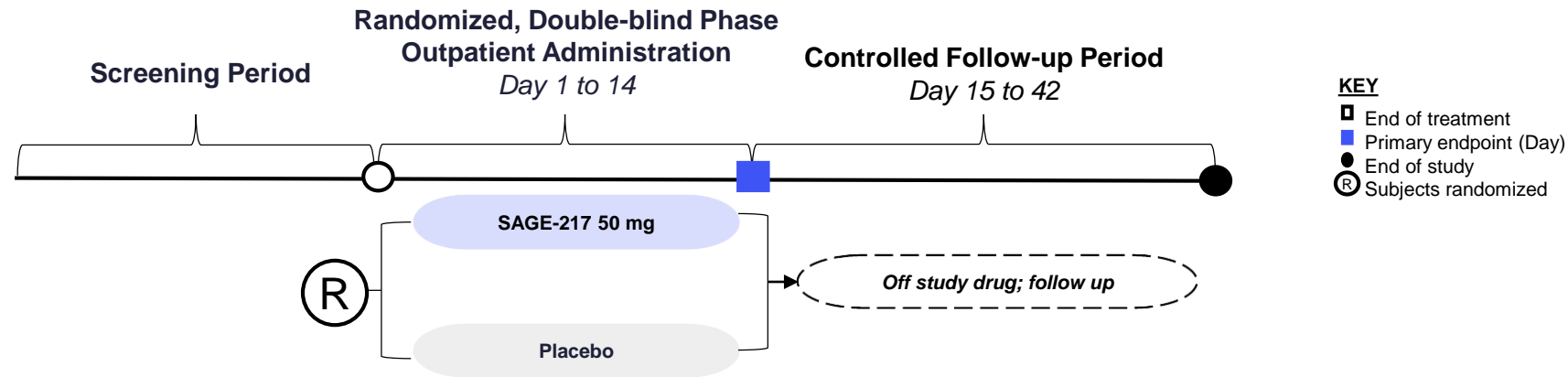
<b>Status</b>	Completed		
<b>Indication</b>	Huntington's Disease Cognitive Impairment	<b>Inclusion Criteria</b>	<ul style="list-style-type: none"> <li>Positive for mutant <i>HTT</i> (documented CAG repeats <math>\geq 36</math> units)</li> <li>Total Functional Capacity (TFC) score <math>&gt; 6</math></li> <li>Score 28 or less on the MoCA at Screening</li> </ul>
<b>Phase</b>	Phase 1		
<b>Start/End Date*</b> <small>*topline data announced</small>	Jan. 2019 / Dec. 2019	<b>Exclusion Criteria</b>	<ul style="list-style-type: none"> <li>Unstable co-morbid medical conditions</li> </ul>
<b>Arms</b>	Open-label SAGE-718 1 mg oral solution	<b>Primary Endpoint</b>	<ul style="list-style-type: none"> <li>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).</li> </ul>
<b>Dosing Regimen</b>	2-week, once daily	<b>Secondary and Other Endpoints</b>	<ul style="list-style-type: none"> <li>PK profile of SAGE-718 following administration of multiple doses of SAGE-718 oral solution</li> <li>Change from baseline on a computerized cognitive battery</li> </ul>

# Study Design:

Planned / Ongoing Studies

# Zuranolone (SAGE-217) - 50 mg

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

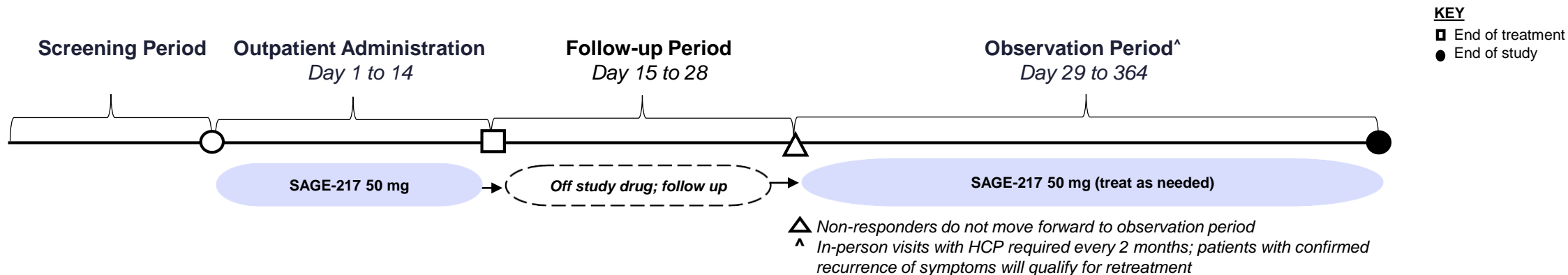


### STUDY OVERVIEW

<b>Status</b>	Planned 2020 Initiation		
<b>Indication</b>	MDD	<b>Inclusion Criteria</b>	<ul style="list-style-type: none"> <li>• Diagnosis of MDD with symptoms that have been present for at least a 4-week period</li> <li>• HAM-D total score <math>\geq 24</math> at screening and Day 1 (prior to dosing)</li> </ul>
<b>Phase</b>	Phase 3	<b>Exclusion Criteria</b>	<ul style="list-style-type: none"> <li>• Active psychosis</li> <li>• Attempted suicide associated with the current episode of MDD</li> <li>• Medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder</li> </ul>
<b>Start/End Date</b>	May 2020 / TBA	<b>Primary Endpoint</b>	<ul style="list-style-type: none"> <li>• Change from baseline in HAM-D total score at Day 15</li> </ul>
<b>Arms</b>	Double-blind, randomized: 1:1 • SAGE-217 50 mg, placebo	<b>Secondary Endpoints</b>	<ul style="list-style-type: none"> <li>• Change from baseline in HAM-D, HAM-A, MADRS, CGI-I, CGI-S</li> <li>• Incidence and severity of AE/SAE</li> </ul>
<b>Dosing Regimen</b>	2-week, once-nightly		

# Zuranolone (SAGE-217) - 50 mg

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



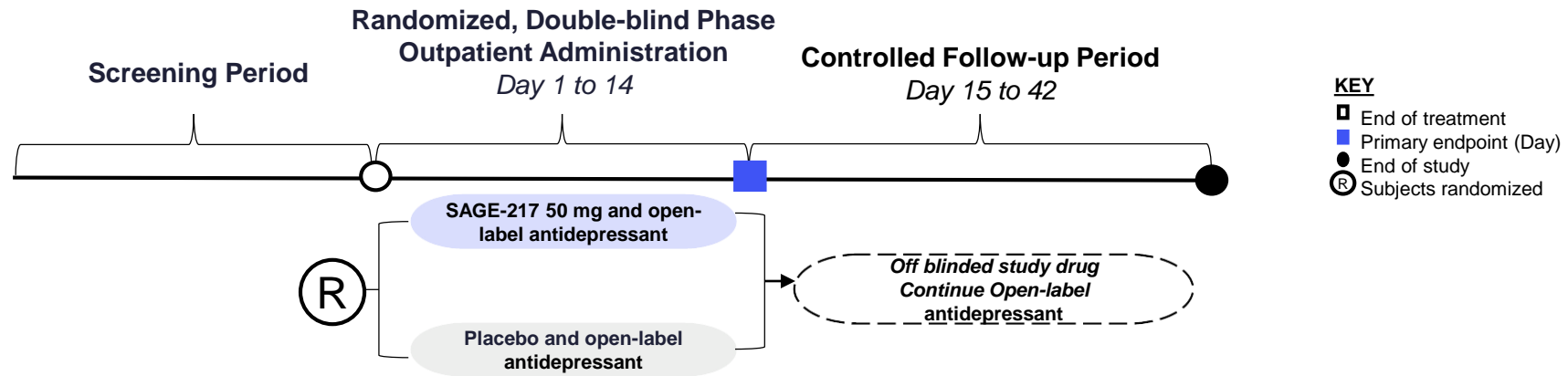
50 mg will be examined in subjects having already received 30 mg, as well as enrollment of a new cohort of 50 mg only subjects

### STUDY OVERVIEW

<b>Status</b>	Enrollment Complete (3Q 2019)	<b>Inclusion Criteria</b>	<ul style="list-style-type: none"> <li>MDD, as diagnosed by SCID-5-CT, with symptoms that have been present for at least a 4-week period</li> <li>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</li> </ul>
<b>Data Timing</b>	TBA	<b>Exclusion Criteria</b>	<ul style="list-style-type: none"> <li>Attempted suicide associated with the current episode of MDD</li> <li>Medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder</li> <li>Subject has had vagus nerve stimulation, electroconvulsive therapy, or has taken ketamine (including esketamine) within the current major depressive episode</li> </ul>
<b>Arms</b>	Non-randomized; SAGE-217 50 mg	<b>Primary Endpoint</b>	<ul style="list-style-type: none"> <li>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*</li> </ul>
<b>Dosing Regimen</b>	2-week, once-nightly	<b>Secondary Endpoints</b>	<ul style="list-style-type: none"> <li>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*</li> <li>Response of initial treatment and/or retreatment, as assessed by:               <ul style="list-style-type: none"> <li>Change from baseline in HAM-D, CGI-S*</li> <li>Percent of subjects achieving: HAM-D response (<math>\geq 50\%</math> reduction) and HAM-D remission (HAM-D total score <math>\leq 7</math>) at the end of each 14-day treatment period*</li> <li>Percent of subjects achieving CGI-I*</li> </ul> </li> </ul>

# Zuranolone (SAGE-217) - 50 mg

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



### STUDY OVERVIEW

<b>Status</b>	Planned 2020 Initiation		
<b>Indication</b>	MDD	<b>Inclusion Criteria</b>	<ul style="list-style-type: none"> <li>• Diagnosis of MDD with symptoms that have been present for at least a 4-week period</li> <li>• HAM-D total score <math>\geq 24</math> at screening and Day 1 (prior to dosing)</li> </ul>
<b>Phase</b>	Phase 3	<b>Exclusion Criteria</b>	<ul style="list-style-type: none"> <li>• Active psychosis</li> <li>• Attempted suicide associated with the current episode of MDD</li> <li>• Medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder</li> </ul>
<b>Start/End Date</b>	TBA	<b>Primary Endpoint</b>	<ul style="list-style-type: none"> <li>• Change from baseline in HAM-D total score at Day 15</li> </ul>
<b>Arms</b>	Double-blind, randomized: 1:1 <ul style="list-style-type: none"> <li>• SAGE-217 50 mg, placebo added to open-label antidepressant</li> </ul>	<b>Secondary Endpoints</b>	<ul style="list-style-type: none"> <li>• Change from baseline in HAM-D, HAM-A, MADRS, CGI-I, CGI-S</li> <li>• Incidence and severity of AE/SAE</li> </ul>
<b>Dosing Regimen</b>	2-week, once-nightly		

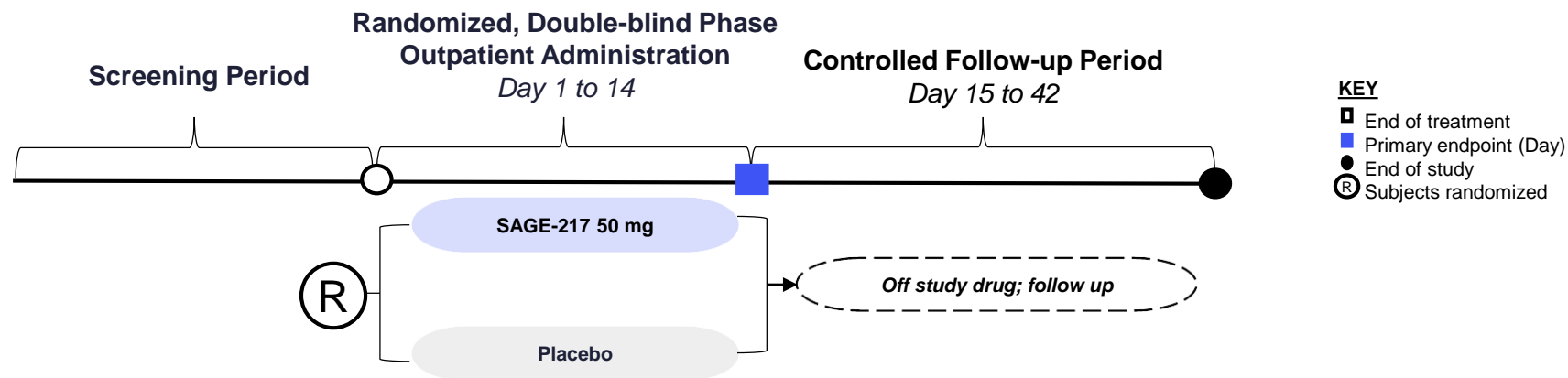


Use of antidepressants, antianxiety or insomnia medications restricted during controlled follow-up period

RRT = rapid response therapy

# Zuranolone (SAGE-217) - 50 mg

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



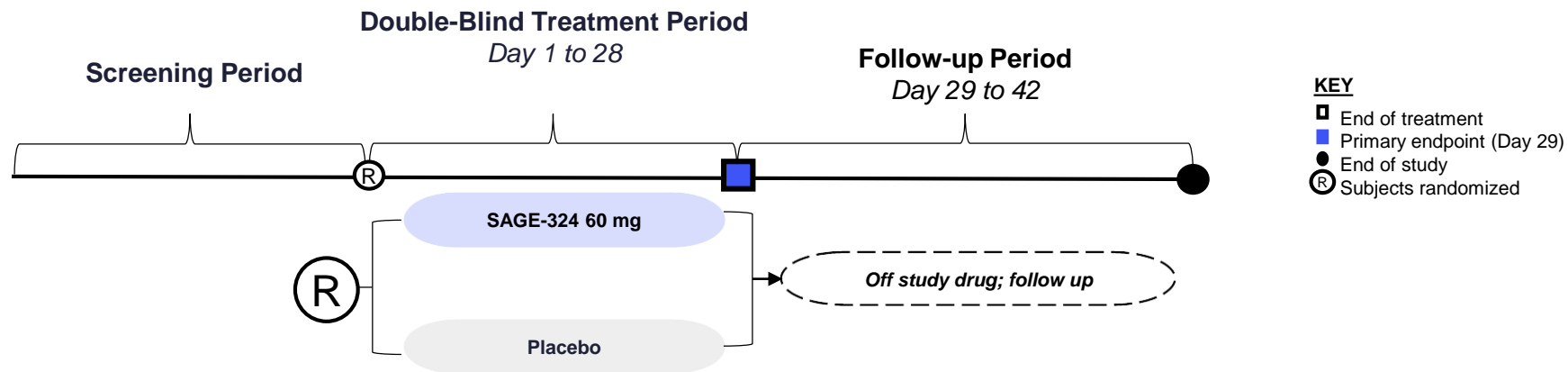
### STUDY OVERVIEW

<b>Status</b>	Planned 2020 Initiation	<b>Inclusion Criteria</b>	<ul style="list-style-type: none"> <li>• Diagnosis of MDD with symptoms that have been present for at least a 4-week period</li> <li>• HAM-D total score <math>\geq 26</math> at screening and Day 1 (prior to dosing)</li> </ul>
<b>Indication</b>	PPD	<b>Exclusion Criteria</b>	<ul style="list-style-type: none"> <li>• Active psychosis</li> <li>• Attempted suicide associated with the current episode of PPD</li> <li>• Medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder</li> </ul>
<b>Phase</b>	Phase 3	<b>Primary Endpoint</b>	<ul style="list-style-type: none"> <li>• Change from baseline in HAM-D total score at Day 15</li> </ul>
<b>Start/End Date</b>	Jun. 2020 / TBA	<b>Secondary Endpoints</b>	<ul style="list-style-type: none"> <li>• Change from baseline in HAM-D, HAM-A, MADRS, CGI-I, CGI-S</li> <li>• Incidence and severity of AE/SAE</li> </ul>
<b>Arms</b>	Double-blind, randomized: 1:1 • SAGE-217 50 mg, placebo		
<b>Dosing Regimen</b>	2-week, once-nightly		



# SAGE-324

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



### KEY

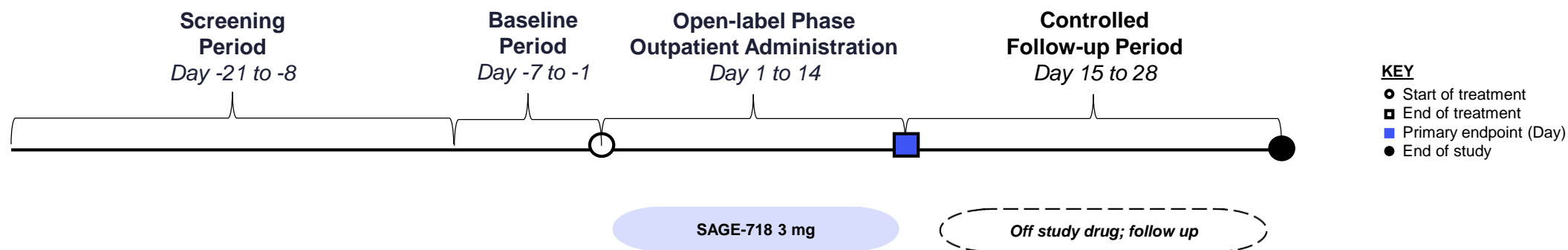
- End of treatment
- Primary endpoint (Day 29)
- End of study
- Ⓡ Subjects randomized

### STUDY OVERVIEW

<b>Status</b>	Ongoing		
<b>Indication</b>	Essential Tremor (ET)	<b>Inclusion Criteria</b>	<ul style="list-style-type: none"> <li>• Diagnosis of ET consisting of               <ul style="list-style-type: none"> <li>• bilateral upper limb action tremor</li> <li>• at least 3 years duration</li> <li>• with or without tremor in other locations</li> <li>• absence of other neurological signs, sudden onset or evidence of stepwise deterioration of tremor</li> </ul> </li> <li>• 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</li> </ul>
<b>Phase</b>	Phase 2	<b>Exclusion Criteria</b>	<ul style="list-style-type: none"> <li>• Presence of known causes of enhanced physiological tremor</li> <li>• Recent exposure to tremorigenic drugs or presence of alcohol withdrawal state</li> <li>• Direct or indirect injury or trauma to the nervous system within 3 months before the onset of tremor</li> <li>• Previous procedure for the treatment of ET, deep brain stimulation, brain lesioning, or magnetic resonance guided procedure</li> </ul>
<b>Start/End Date</b>	TBA	<b>Primary Endpoint</b>	<ul style="list-style-type: none"> <li>• Change from baseline in TETRAS performance subscale part 4 upper limb tremor score on Day 29</li> </ul>
<b>Arms</b>	Double-blind, randomized: 1:1 • SAGE-324 60 mg: placebo	<b>Secondary Endpoints</b>	<ul style="list-style-type: none"> <li>• Change from baseline in TETRAS performance subscale part 4 upper limb tremor score at all other timepoints</li> <li>• Change from baseline in Kinesia ONE accelerometer scores</li> </ul>
<b>Dosing Regimen</b>	28 days, once-daily		

# SAGE-718

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



### STUDY OVERVIEW

<b>Status</b>	Start-up	<b>Inclusion Criteria</b>	<ul style="list-style-type: none"> <li>• Diagnosis of Parkinson's Disease Mild Cognitive Impairment</li> <li>• Score 20 to 25 (inclusive) on the MoCA at Screening</li> </ul>
<b>Indication</b>	PD-MCI		
<b>Phase</b>	Phase 2	<b>Exclusion Criteria</b>	<ul style="list-style-type: none"> <li>• Diagnosis of dementia of any etiology</li> <li>• Experiencing fluctuations in motor and/or non-motor symptoms of Parkinson's disease</li> </ul>
<b>Start/End Date</b>	TBA		
<b>Arms</b>	Open-label SAGE-718 3 mg oral tablet	<b>Primary Endpoint</b>	<ul style="list-style-type: none"> <li>• Incidence of treatment-emergent adverse events (TEAEs)</li> </ul>
<b>Dosing Regimen</b>	2-week, once daily	<b>Secondary and Other Endpoints</b>	<ul style="list-style-type: none"> <li>• Change from baseline in vital signs, clinical laboratory analytes, electrocardiograms, and responses on the Columbia–Suicide Severity Rating Scale (C-SSRS)</li> <li>• Change from baseline on comprehensive neurocognitive and neuropsychiatric batteries</li> </ul>