Sage Therapeutics™

Investor Presentation

February 2021

Safe Harbor Statement

- The slides presented today and the accompanying oral presentations contain forward-looking statements, which may be identified by the use of words such as “may,” “might,” “will,” “should,” “can,”,“expect,” “plan,” “anticipate,” “believe,” “estimate,” “project,” “intend,” “future,” “opportunity”, “goal”, “mission”, “potential,” or “continue,” and other similar expressions.
- Forward-looking statements in this presentation include statements regarding: our clinical development plans, including expected timelines for initiation and completion of trials and reporting of results; the potential regulatory pathways for our product candidates; our belief in the potential for success of our product candidates in various indications, including 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 that we hope to help; the goals, opportunity and potential for our business; our views with respect to potential value creation opportunities, including the potential benefits and results that may be achieved through our collaboration with Biogen; our plans for advancing, accelerating and expanding our development efforts and the output of our product engine; our belief in the potential for upcoming catalysts and milestones to support our mission of bringing innovative medicines to help millions of patients and their families; our expectations with respect to 2021 year-end cash; and our belief in our ability to become the leading brain health company with multiple franchises.
- 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:
  - Our clinical trials may not meet their primary endpoints or key secondary endpoints. Success in non-clinical studies or in prior clinical trials of our product candidates may not be repeated or observed in ongoing, planned or future studies involving the same compound or other product candidates. Final results of studies where we reported interim results may not be consistent with the interim results. Non-clinical and clinical results from ongoing or future trials 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.
  - We may experience slower than expected enrollment in our clinical trials or may encounter other delays or problems, including in analyzing data or requiring the need for additional analysis, data or patients, and such issues with any trial could cause delay in completion of the trial, availability of results and timing of future activities.
  - The impact of COVID-19 on our clinical development timelines 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 cause us to have to change our plans.
  - 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 ongoing and planned 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 and other regulatory authorities may ultimately decide that the design or results of our completed, ongoing or 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 despite prior regulatory advice. At any stage, regulatory authorities may ask for additional clinical trials, nonclinical studies or other data in order for us to proceed further in development or to file for or obtain regulatory approval, and we may not be successful in those efforts. Other decisions or actions of the FDA or other regulatory authorities may affect the initiation, timing, design, size, progress and cost of clinical trials and our ability to proceed with further development;
  - We may never achieve the rate of new product candidates from our product engine that we expect in the future.
  - 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.
  - The anticipated benefits of our collaboration with Biogen may never be achieved
  - 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 ours patent portfolio against challenges from third parties.
  - We may face competition from others developing products for similar uses as those for which our product candidates are being developed.
  - Our operating expenses may be higher than forecasted, and we may also face unexpected expenditures which could cause us to change our plans, and as a result, our expectations as to year-end cash may prove not to be correct.
  - We may not be able to establish and maintain key business relationships with third parties on we may encounter technical and other unexpected hurdles in the manufacture and development of our products.
  - Any of the foregoing or other factors may negatively impact our ability to achieve our goals, mission, opportunities, plans or expectations for our business.
- For additional disclosure regarding these and other risks Sage faces, see the disclosure contained in the "Risk Factors" section of our most recent 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™

Sage is a leader in brain health – *making medicines that matter*

- Advancing Brain Health Leadership
- Mission to be a top-tier biopharmaceutical company in the next 5 years
- Rich pipeline across 3 franchises
  - First and only product approved specifically for postpartum depression
  - Two late-stage programs; four ongoing phase 3 studies
  - 5 NCE development programs across 9+ indications
  - Strong intellectual property strategy
- Goal of 2 or more IND-enabling programs per year by 2023
- Catalyst rich 2021; expected topline readouts from ten clinical trials
- $2B+ capital to fund efforts to accelerate and advance medicines that have potential to impact an estimated > 450M patients globally

Sage Therapeutics™

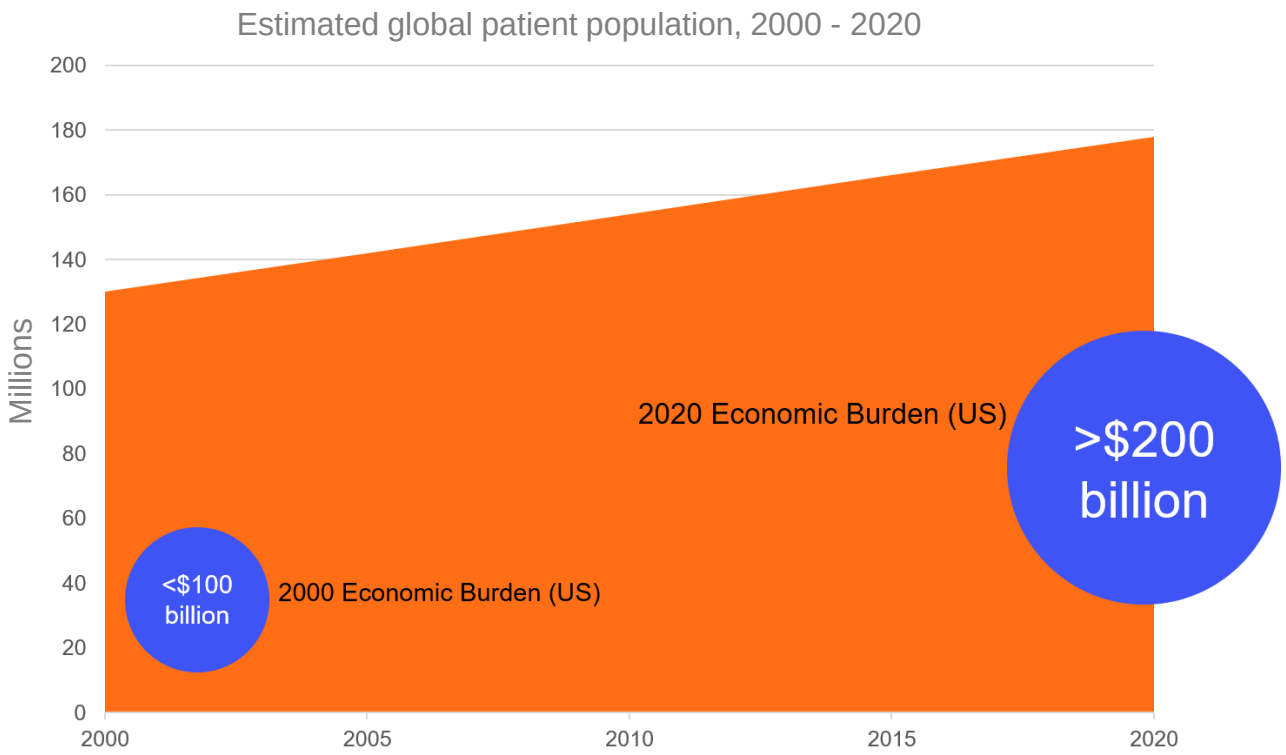
A Leading Brain Health Portfolio

Light shades indicate trials in the planning or evaluation stage

Depression & Mood Disorders

Depression and Mood Disorders

- Despite new classes of medicines developed to treat depression in last 60 years, **prevalence and impact continue to increase globally**
  - > 50% of patients suffer **severe impact on ability to function**
  - Depression shown to **have generational impact** as well as direct impact on caregivers (e.g., caregivers/ partners unable to work full time, increasing economic burden exponentially)
  - Rates continue to increase, particularly in young adults
- Increasing evidence that depression and some **mood disorders are episodic events** caused by many triggers (e.g., genetics, postpartum, COVID)
- Sage believes patients can be **treated episodically and/or as needed, reducing burden of chronic management**



BLS CPI (Consumer Price Index) Calculator was used to estimate 2000 and 2020 economic burden using U.S. specific studies in respect to the indications noted.

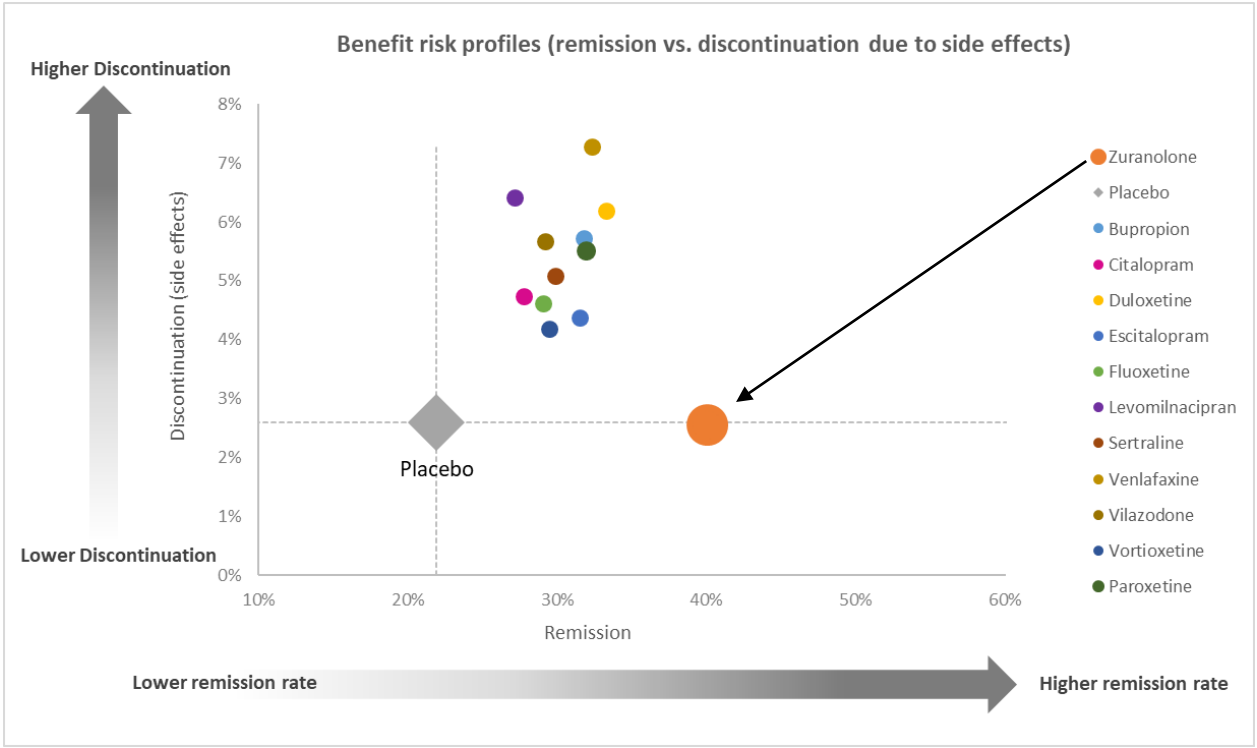
Abbreviations: PPD = postpartum depression, MDD = major depressive disorder, TRD = treatment resistant depression, GAD = generalized anxiety disorder, BPD = bipolar depression

Sage Therapeutics™

Paucity of innovation plagues patient journey to find effective treatment for depression and other mood disorders

- Benefit/risk profile of treatments for major depressive disorder remains unchanged despite at least 35 approved treatments in last 30 years
- Increasing burden and unmet need supports development of more innovative treatments
- In clinical trials to date:
  - Zuranolone demonstrated a reduction of depressive symptoms seen within 72 hours
  - 70% of subjects treated with zuranolone in the SHORELINE study interim data cut (30 mg) **required 2 or fewer treatments** in a year
  - **Zuranolone has been generally well-tolerated** in more than 3,000 subjects to date

Benefit (remission) vs. Risk (discontinuation)
(integrated set 201B & MOUNTAIN ≥24 compared to SoC)



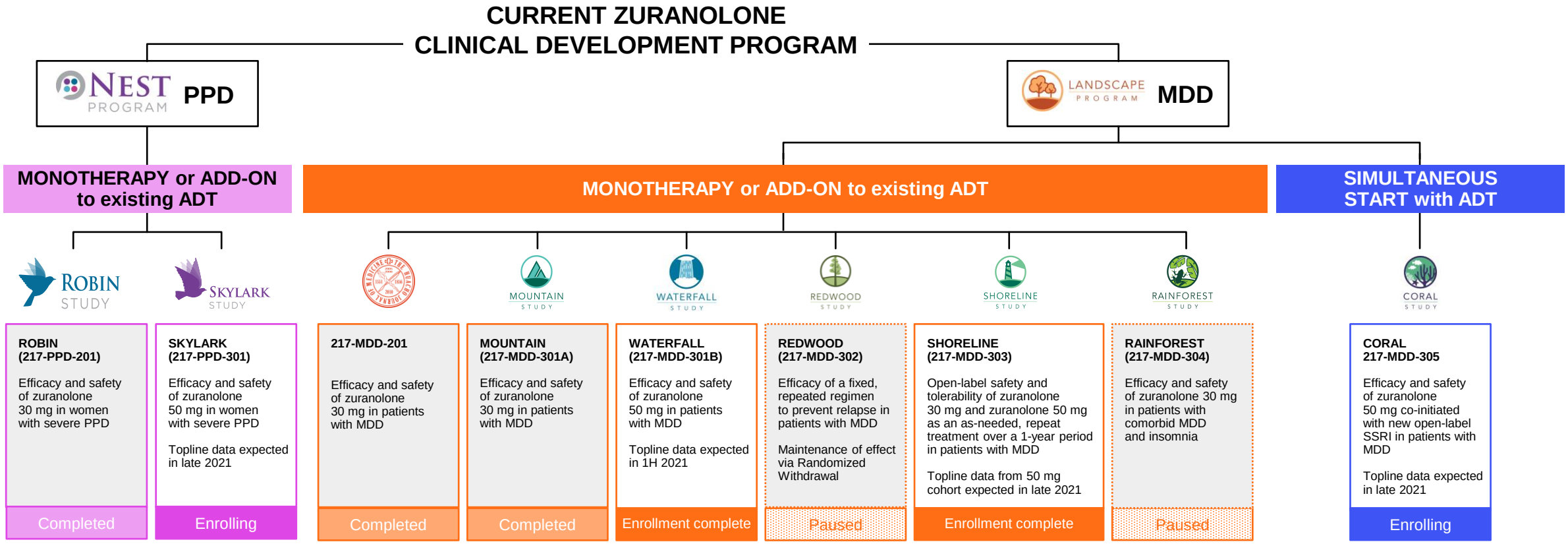
Comparison to SOC was carried out through a Bucher ITC using Cipriani 2018[1]. There are assumptions and limitations associated with this analysis.

Variations in study design across the included trials may limit the generalizability of results.

[1]Cipriani, 2018 Lancet

Zuranolone's Landscape Program

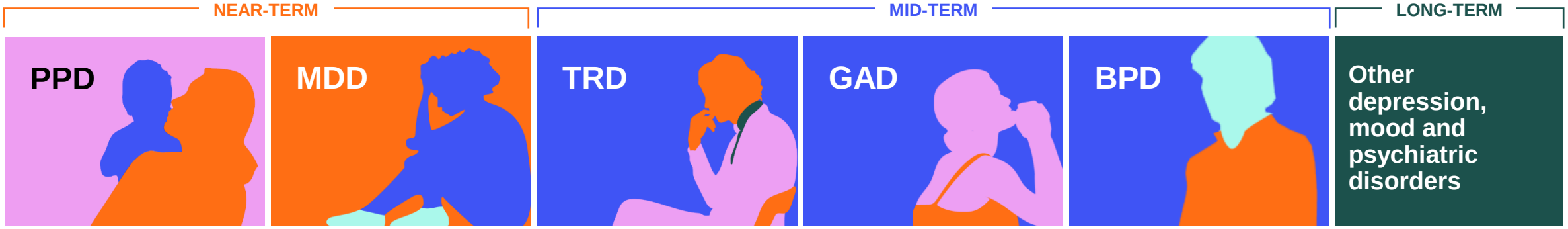
Potential to reshape the depression landscape



Abbreviations: PPD = postpartum depression, MDD = major depressive disorder, ADT = antidepressant therapy

Zuranolone is a Sage-created innovation with potential to impact millions globally

Development plan has potential to be accelerated by strategic collaboration with Biogen



	2021 Early	2021 Mid	2021 Late	*Early:Q1-Q2; Mid:Q2-Q3; Late: Q3-Q4
DEPRESSION FRANCHISE				**Expected milestones:**
Zuranolone (Sage-217)		●		Report topline data from WATERFALL Study in major depressive disorder **(1H21)**
		●		Report full data from SHORELINE Study 30 mg cohort in major depressive disorder
			●	Report topline data from SKYLARK Study in postpartum depression
			●	Report topline data from CORAL Study in major depressive disorder for rapid response treatment when co-initiated with new antidepressant therapy
			●	Report topline data from SHORELINE Study 50 mg cohort in major depressive disorder

Composition of Matter Patent through 2034, subject to potential extensions

Sage Therapeutics™ Biogen SHIONOGI

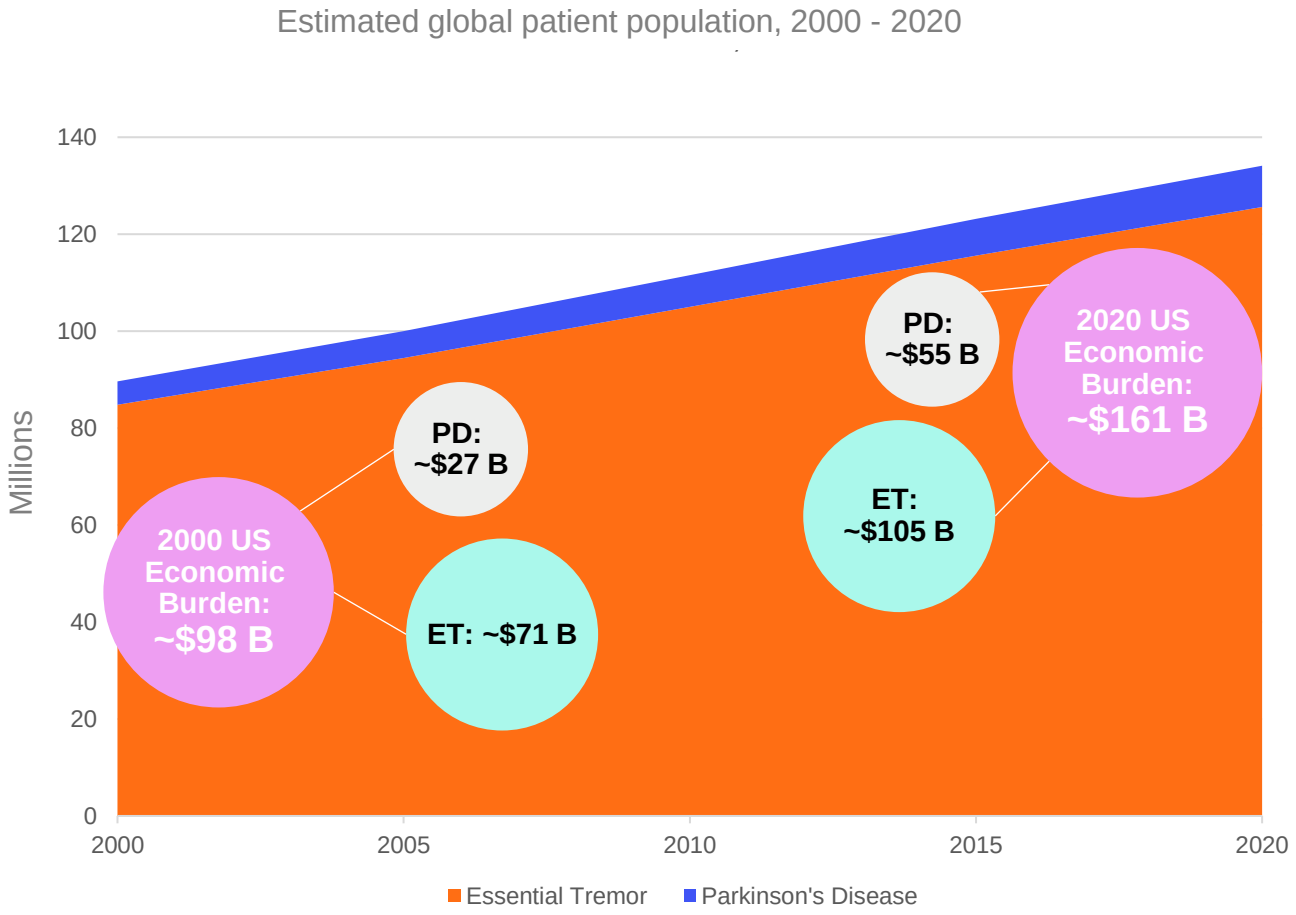
Abbreviations: PPD = postpartum depression, MDD = major depressive disorder, TRD = treatment resistant depression, GAD = generalized anxiety disorder, BPD = bipolar depression

Neurology Franchise

Movement and neurological disorders

Gaps remain in bringing effective treatments to people with movement disorders

- Standards of care are inadequate for many people suffering from debilitating movement disorders
  - It's estimated that nearly 135 million people globally suffer from essential tremor (ET) or Parkinson's disease (PD)
- Movement disorders can make the simplest activities of daily life difficult, if not impossible
  - Chewing, eating, standing, walking, self-care
- Substantial mental health impact and caregiver burden
  - Depression/low mood, anxiety, poor sleep
- Sage has demonstrated that the GABA positive allosteric modulation mechanism is important in movement disorders



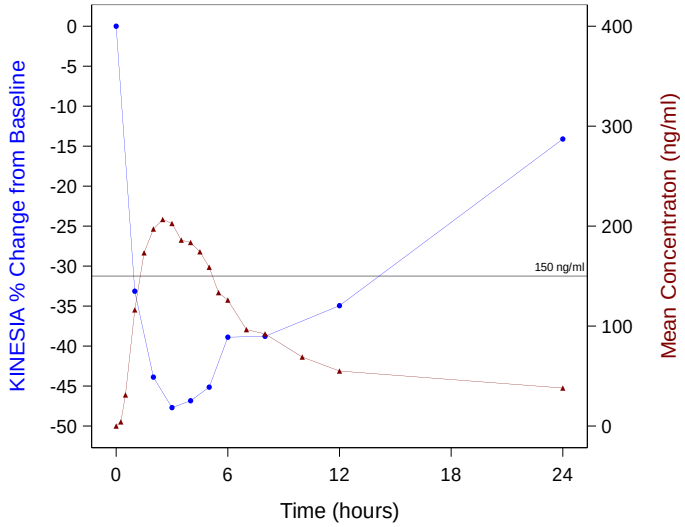
BLS CPI (Consumer Price Index) Calculator was used to estimate 2000 and 2020 economic burden using U.S. specific studies in respect to the indications noted.

SAGE-324: Novel potential treatment for movement disorders

Predictable PD effects and PK profile with long half-life

- SAGE-324 is well-suited for development in essential tremor (ET):
  - Most prevalent movement disorder in the US (est. 6M+)
  - Last pharmacological treatment for ET was approved in 1967
  - High unmet need; 50% of treated patients do not respond or have sub-optimal response to standard of care
- In an open-label, phase 1 study, a single dose of SAGE-324 resulted in nearly 50% tremor reduction in ET patients, demonstrated on measure most closely associated with disability
- Good oral bioavailability and long half-life provides flexibility in dosing paradigms for potential development in additional disorders including Parkinson's disease and epilepsies

Total upper limb combined score after single dose in 6 people with ET as measured by accelerometer



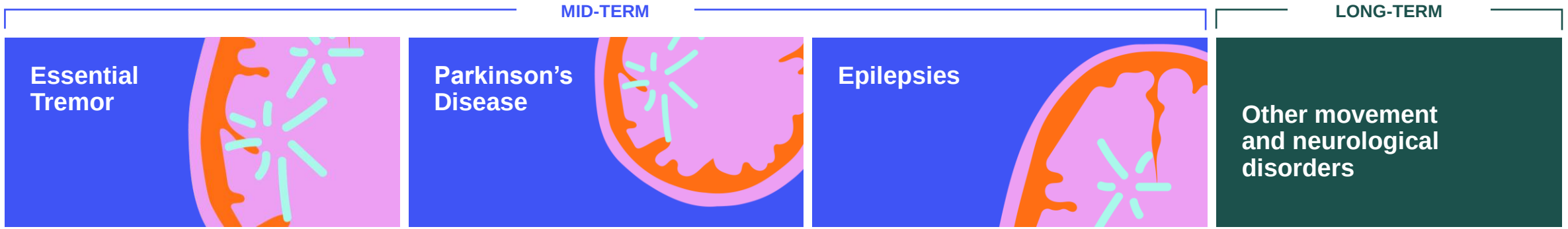
PK over time in 6 people with ET dosed with SAGE-324

- Clear PK/PD relationship
- Promising signals of tremor reduction, consistent with those observed previously for brexanolone and SAGE-217
- Well-tolerated in Phase 1 study: most common AEs (≥5%) included somnolence, dizziness, and feeling of relaxation

Sage Therapeutics™ Biogen

Sage-created innovation with potential to impact millions globally

Development plan has potential to be accelerated by strategic collaboration with Biogen



2021

	Early	Mid	Late	**Early:Q1-Q2; Mid:Q2-Q3; Late: Q3-Q4*
NEUROLOGY FRANCHISE				**Expected milestones:**
SAGE-324	●			Report topline data from KINETIC Study in essential tremor
			●	Initiate Phase 2b study in essential tremor to explore dose and frequency, including potential formulations

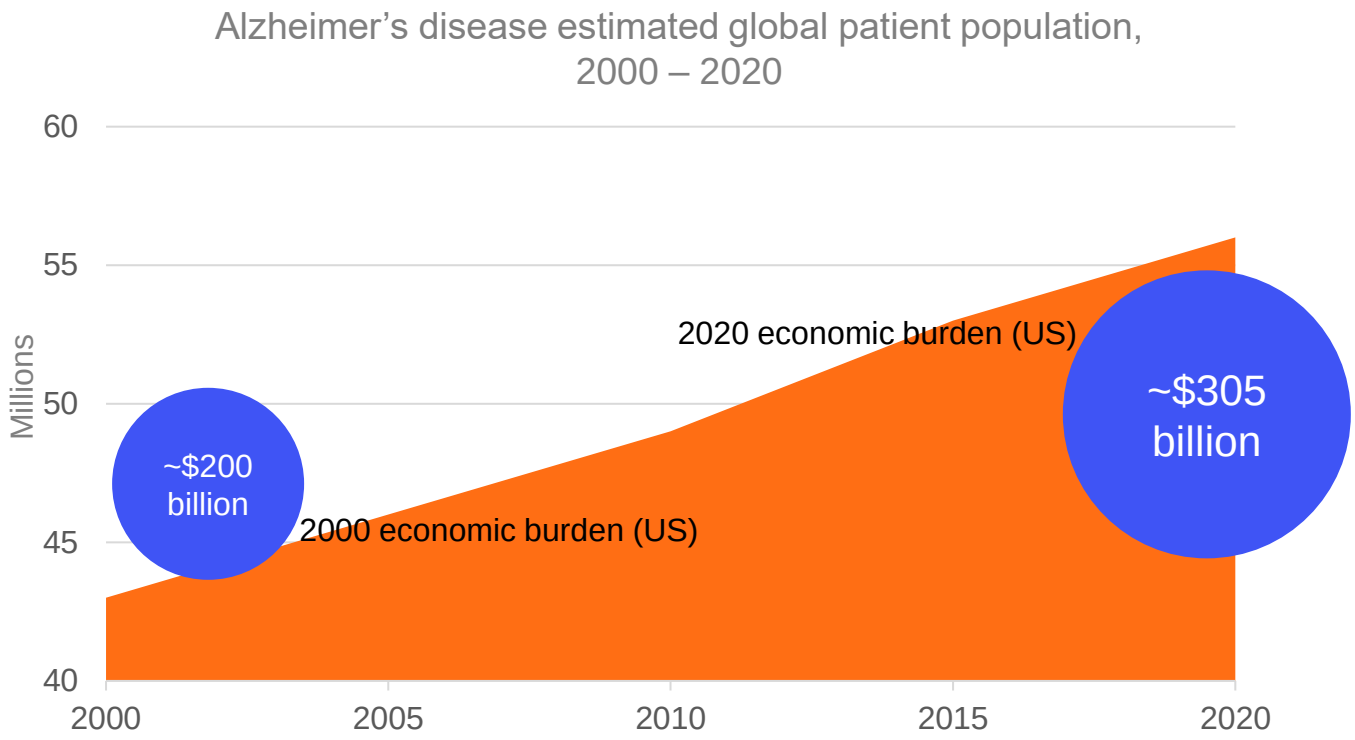
Sage Therapeutics™ Biogen

Neuropsychiatry Franchise

Neuropsychiatric Disorders

Dearth of innovative treatments approved for disorders of cognition

- Globally, disorders involving cognitive dysfunction continue to increase and are one of the greatest areas of unmet need
  - Currently available treatments are limited in efficacy
- People with cognitive impairment report:
  - Executive deficits: multi-tasking, organization, planning, working memory
  - Difficulty concentrating
  - Memory loss
- Significant impact on patient ability to work, live independently, adhere to medical care, and interact with family



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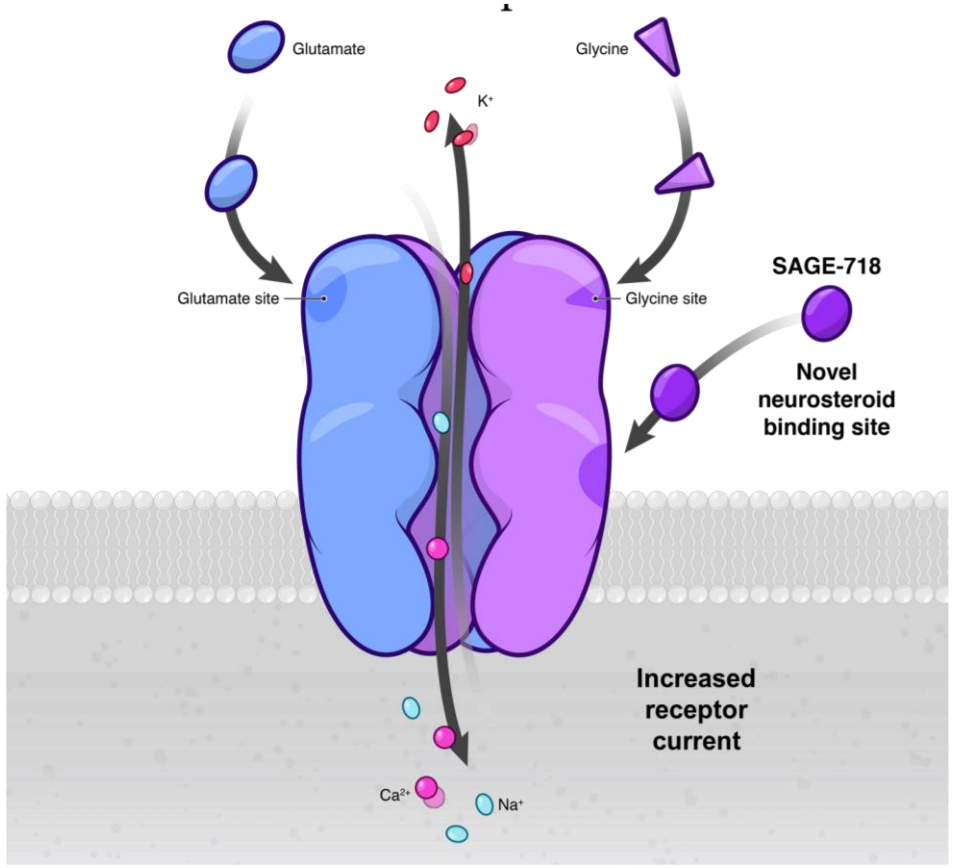
BLS CPI (Consumer Price Index) Calculator was used to estimate 2000 and 2020 economic burden using U.S. specific studies in respect to the indications noted.

Re-thinking Treatment of Neuropsychiatric Disorders

Sage has developed a robust library of NMDA receptor modulators

- NMDA receptors play a critical role in the process of neuroplasticity and are important in a host of cognitive, learning and behavioral processes
  - NMDA receptor function can be reduced by disease and declines during aging
- NMDA positive allosteric modulators (PAMs) may have potential to address disorders of cognition & behavior across the lifespan:
  - Neurodegenerative disorders
  - Neurodevelopmental disorders
  - Disorders requiring recovery or rehabilitation of cognitive function
- Sage has developed a library of novel, wholly-owned, NMDA modulators with unique profiles, including SAGE-718
- Biomarkers identified by Sage may inform development

Endogenous & Exogenous Ligands at the NMDA Receptor



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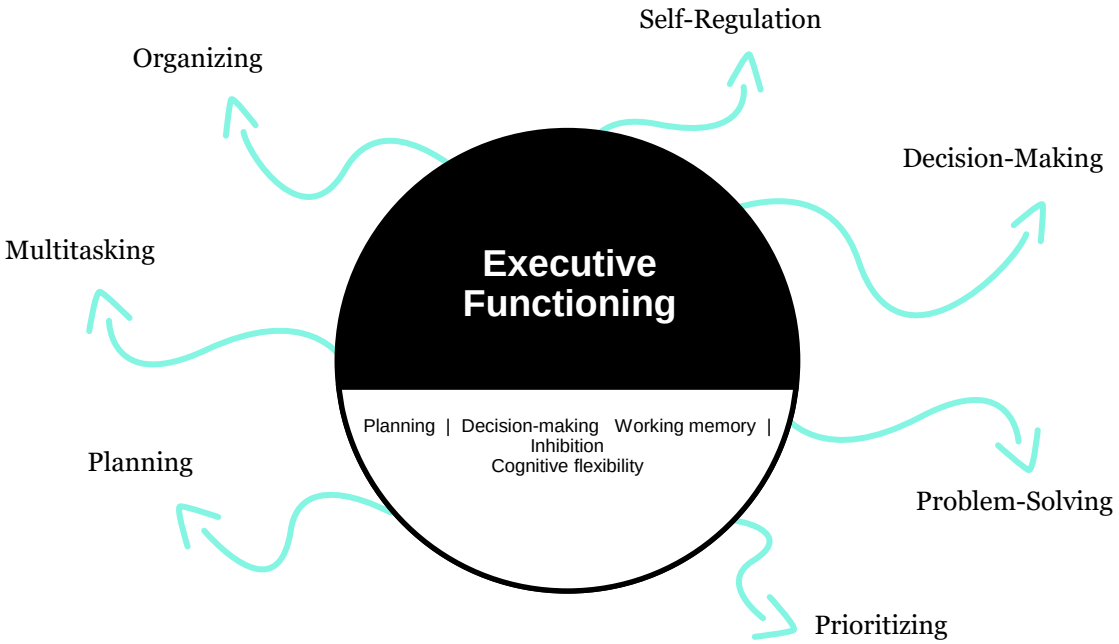
SAGE-718: Improving cognitive and executive function

Potential to provide unique cognitive benefits for patients with neurodegenerative disorders

- SAGE-718 profile well-suited for study of potential to benefit executive function in patients with neurodegenerative disorders:
  - Clinical findings from Phase 1 studies suggest potential to improve executive function, a key component of brain health across life-span
- Ongoing exploration in areas of cognitive dysfunction in diseases with high unmet need, including Alzheimer's, Parkinson's, and Huntington's disease
- Five phase 1 studies to date – generally well-tolerated and with meaningful activity suggesting potential in brain health disorders



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SAGE-718 Data Suggest Potentially Transformational Activity in the Brain

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

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

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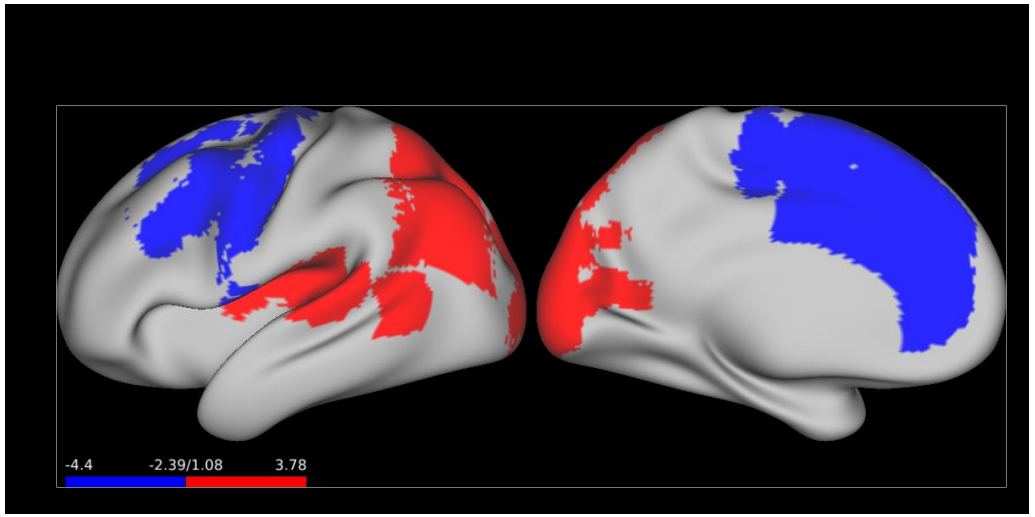
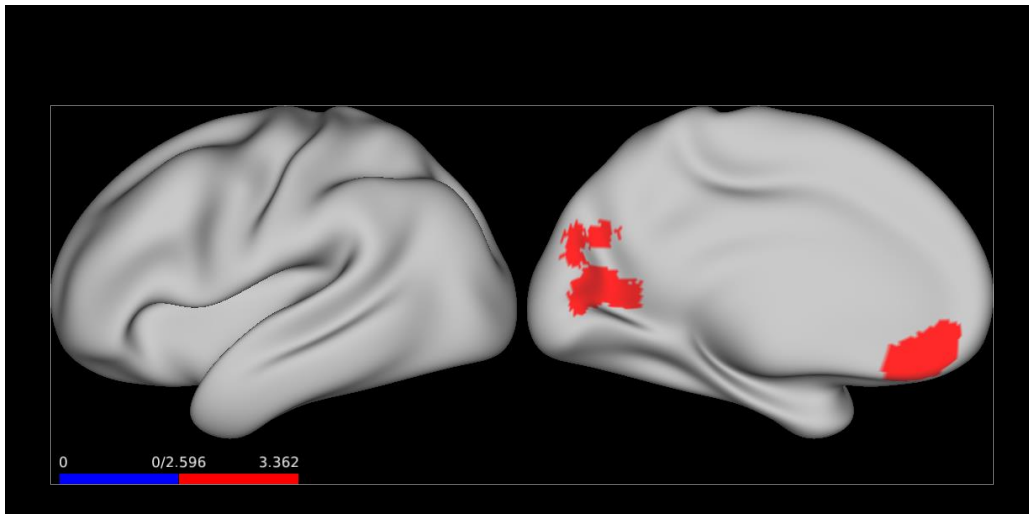
SAGE-718 Attenuated Effects of Ketamine on Brain Circuits, in Phase 1 Study

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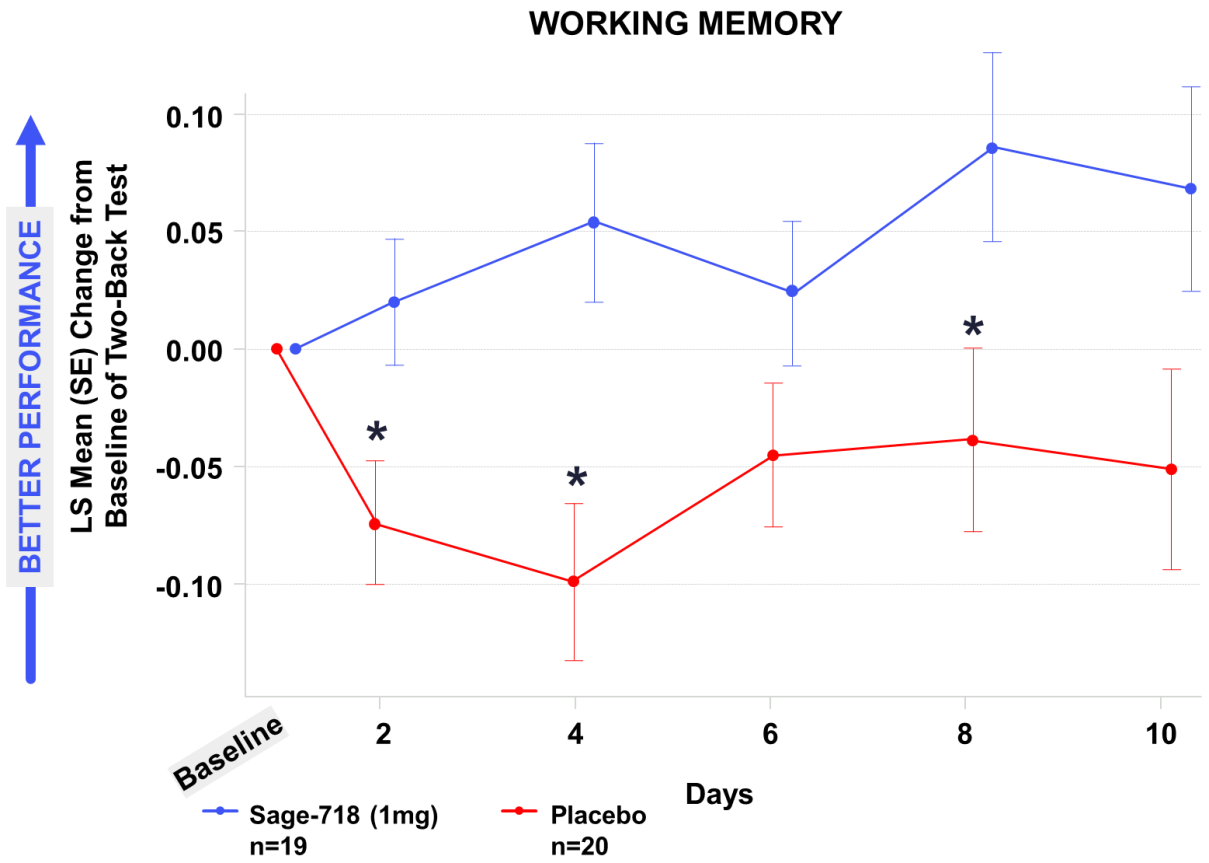
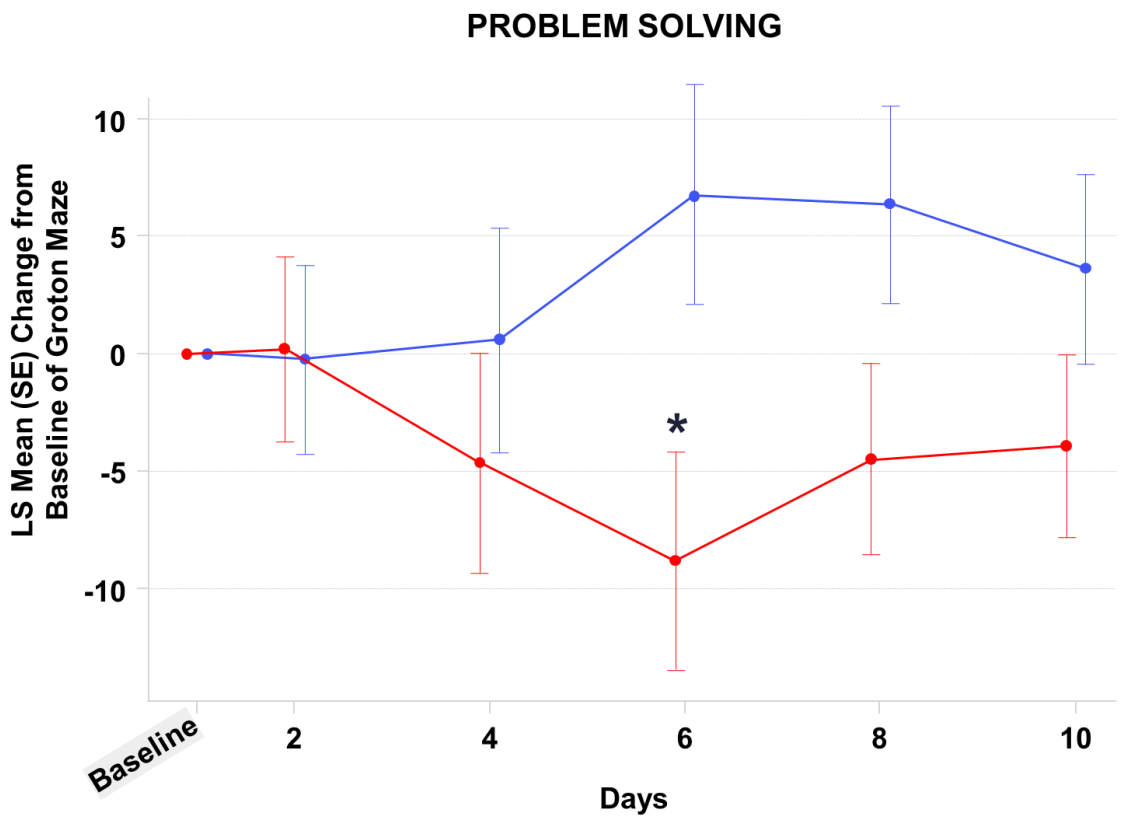
In a Phase 1 Study with Healthy Volunteers SAGE-718 Significantly Improved Executive Functioning





*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.

NMDA PAM

Sage-created innovation with potential to impact millions globally

Collaboration provides resources for acceleration of plans for internal pipeline, including SAGE-718

MID-TERM

LONG-TERM

Parkinson's Disease Cognitive Dysfunction

Alzheimer's Disease Cognitive Dysfunction

Huntington's Disease Cognitive Dysfunction

Other conditions with impaired cognitive/executive dysfunction

2021

	Early	Mid	Late	*Early:Q1-Q2; Mid:Q2-Q3; Late: Q3-Q4
NEUROSPYCHIATRY FRANCHISE				**Expected milestones:**
SAGE-718	●			Report topline data from PARADIGM Study in Parkinson's disease cognitive dysfunction
			●	Report topline data from LUMINARY Study in Alzheimer's disease mild cognitive impairment and mild dementia
			●	Initiate placebo-controlled Phase 2 study

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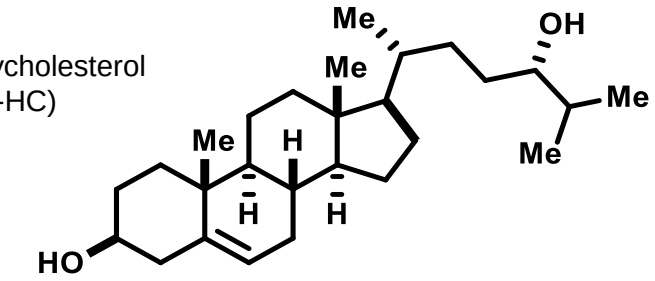
Sage Has Developed a Robust Library of NMDAr Modulators

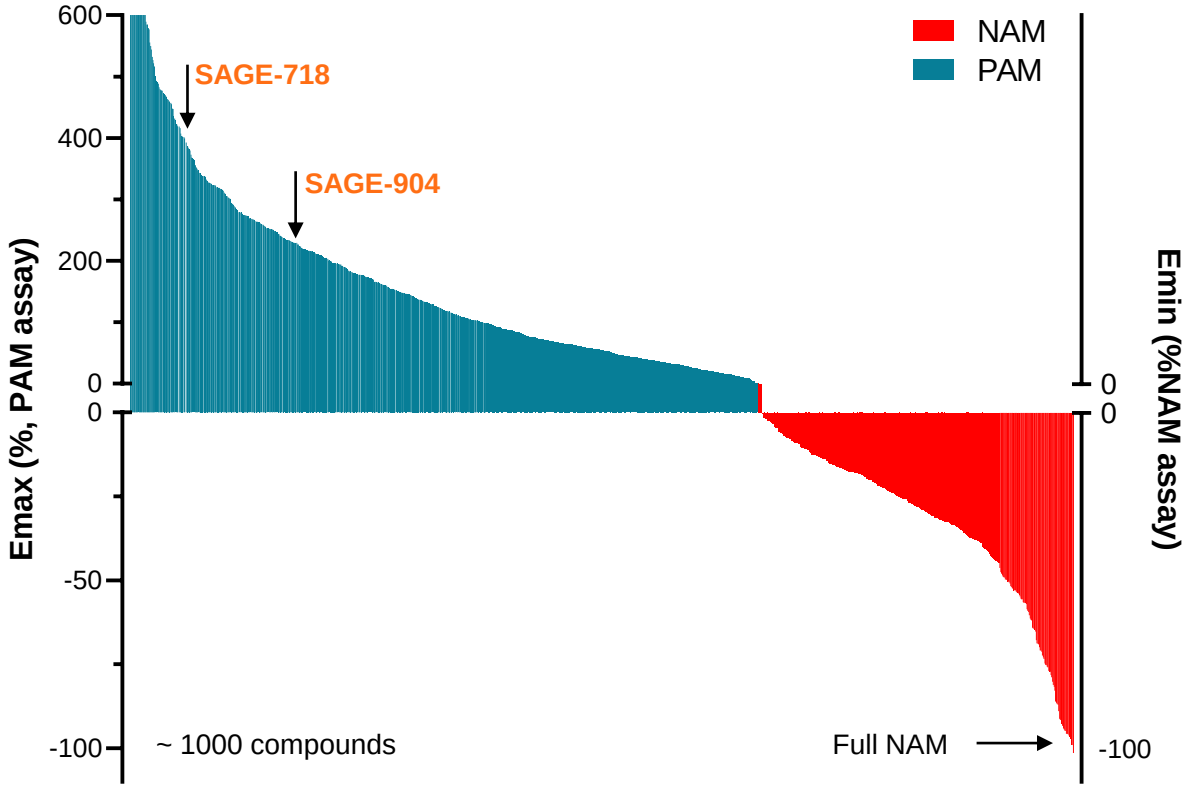
Creating a portfolio of drug-like molecules targeting NMDA receptors

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

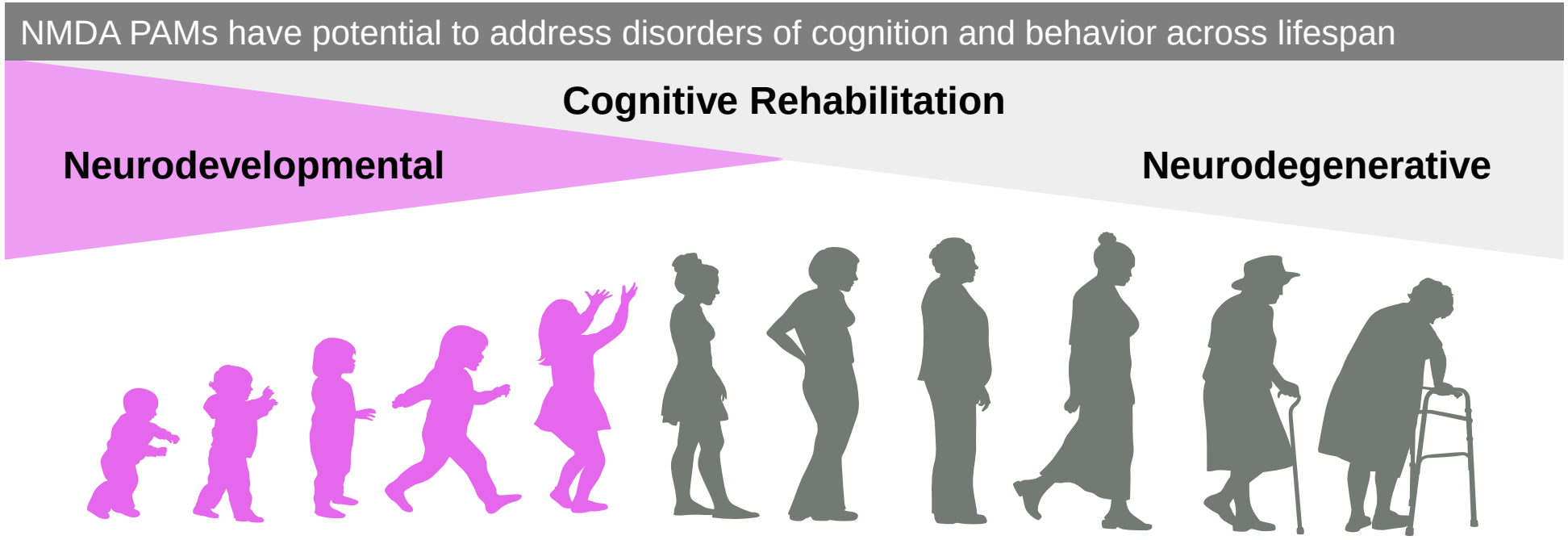
Robust library of novel oxysterol-based NMDA modulators, with unique profiles



Sage proprietary product engine

SAGE-904: Differentiated NMDA PAM profile

Pharmacological profile suited for study in neurodevelopmental therapeutics



- SAGE-904 designed for potential use as ***neurodevelopmental*** therapy
- Druglike profile supporting once-daily, oral, chronic dosing
- Phase 1 studies to inform selection of development path

SAGE-689: Rapid acting, intramuscular GABA PAM

Multiple opportunities in diseases with high unmet need

- Potent preclinical anxiolytic and anticonvulsant activity
- Rapid absorption and good bioavailability following *intramuscular* administration
- Phase 1 translational studies designed to accelerate specific indication selection
- Formulation flexibility and high intrinsic solubility enables multiple potential pathways based on patient needs
  - Acute use with faster onset may provide opportunities in areas like agitation or social anxiety

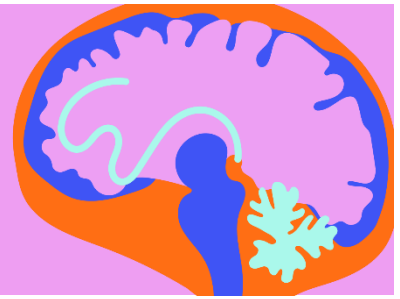
Continuing Innovation with the GABA and NMDA platforms

Preclinical profile of SAGE-319
GABA PAM

- Potent, extra-synaptic $GABA_A$ receptor preferring positive allosteric modulator
- Druglike profile supporting daily, oral, chronic dosing
- Differentiated EEG signature compared to SAGE-217 and SAGE-324

Potential indications:
DISORDERS OF SOCIAL INTERACTION

Preclinical profile of SAGE-421
NMDA PAM



- Potent NMDA receptor positive allosteric modulator
- Druglike profile supporting daily, oral, chronic dosing

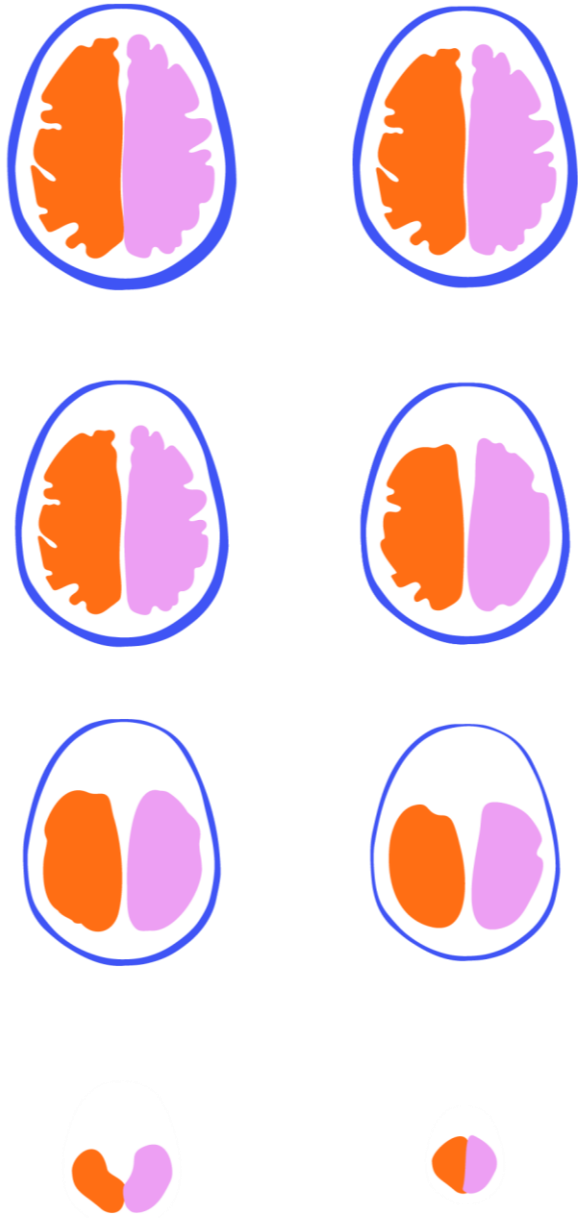
Potential indications:
NEURODEVELOPMENTAL DISORDER

Sage Therapeutics™

Proactive, predictive and productive drug development approach:

Enables product engine and portfolio expansion into diseases with high unmet needs

- Sage is a leader in NAS and oxysterol chemistry with >8K compound library and >50 patent applications
- Focus on understanding how to modify circuitry that impacts brain function at the network level
- Robust engine for turning early ideas into clinical proof-of-concept rapidly



Sage Therapeutics™

Fourth Quarter and Full Year 2020 and 2019 Financial Results

Strong financial position with over $2.1 billion in cash

Item	Q4 ’20	Q4 ’19	Full Year ’20	Full Year ’19
Revenue: • *Zulresso* • *Collaboration*	 *$1.7M* *$1.1B*	 *$2.0M* -	 *$6.7M* *$1.1B*	 *$4.0M* *$2.9M*
R&D Expense	$81.7M	$91.3M	$292.7M	$368.8M
SG&A Expense	$53.5M	$85.1M	$197.0M	$345.8M
Cost of Goods Sold	$0.1M	$0.2M	$0.6M	$0.4M
Restructuring	($0.1M)	-	$27.7M	-
Total Operating Costs and Expenses	$135.2M	$176.6M	$518.0M	$715.0M
Net Income (Loss)	$974.9M	($168.7M)	$606.0M	($680.2M)
Cash and Marketable Securities	$2.1B	$1.0B	$2.1B	$1.0B

Sage anticipates a cash balance of more than $1.7 billion at end of 2021
The Company does not anticipate milestone payments from collaborations in 2021

Sage Therapeutics™

Anticipated 2021 Milestones

*Early:Q1-Q2; Mid:Q2-Q3; Late: Q3-Q4

	Early	Mid	Late	
DEPRESSION FRANCHISE				
Zuranolone (Sage-217)		●		Report topline data from WATERFALL Study in major depressive disorder (1H21)
		●		Report full data from SHORELINE Study 30 mg cohort in major depressive disorder
			●	Report topline data from SKYLARK Study in postpartum depression
			●	Report topline data from CORAL Study for rapid response treatment
			●	Report topline data from SHORELINE Study 50 mg cohort in major depressive disorder
NEUROLOGY FRANCHISE				
SAGE-324	●			Report topline data from KINETIC Study in essential tremor
			●	Initiate Phase 2b study in essential tremor to explore dose and frequency, including potential formulations
NEUROSPYCHIATRY FRANCHISE				
SAGE-718	●			Report topline data from PARADIGM Study in Parkinson's disease cognitive dysfunction
			●	Report topline data from LUMINARY Study in Alzheimer's disease mild cognitive impairment and mild dementia
			●	Initiate placebo-controlled Phase 2 study
EARLY DEVELOPMENT				
SAGE-689			●	Complete Phase 1 SAD study
SAGE-904			●	Complete Phase 1 SAD/MAD studies
OTHER DEVELOPMENT OPPORTUNITIES				
Brexanolone			●	Report topline data from study in COVID-19 related acute respiratory distress syndrome
Product Engine		**By 2023**		Capable of delivering 2+ IND-enabling compounds per year

Sage is a leader in brain health – *making medicines that matter*

Disciplined execution in 2020 created strong foundation for near, mid, and long-term value-creation potential for patients and shareholders

Leading brain health pipeline spanning three core franchises, each with differentiated assets with goal of delivering two or more IND-enabling compounds per year, starting in 2023

Catalyst rich 2021 includes meaningful data flow across all franchises

Expertise in place to focus on successful patient access and global commercial execution if product candidates are approved

Financial flexibility enables continued investment in innovation, with mission of creating top-tier biopharma in 5 years

Sage Therapeutics™

Appendix

Brain Health Disorders — Global Healthcare Challenge

In 10 years, Sage has expanded the potential for solutions and through collaborations expects to further accelerate and expand estimated patient reach

18M
Sage

22M
Sage + Shionogi

>450M
Sage + Shionogi + Biogen
+ potential acceleration of Sage proprietary programs

- Huntington's Disease
- Alzheimer's Disease and other Dementias
- Epilepsy
- Treatment Resistant Depression
- Bipolar Depression
- General Anxiety Disorder
- Parkinson's Disease
- Essential Tremor

- Postpartum Depression
- Major Depressive Disorder

Shionogi Collaboration

2020 Biogen Collaboration

Sage Therapeutics™

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

Strategic Zuranolone and SAGE-324 Collaboration with Biogen

- **50:50 joint development and commercialization of zuranolone and SAGE-324 in the United States**
  - Opportunity to expand the number of indications, patient impact and thereby the commercial value of zuranolone and SAGE-324, assuming successful development
- **Enables expansion and acceleration of pipeline**
  - Financial and operational flexibility from collaboration allows Sage to fully evaluate the potential of existing programs and fuels product engine enabling continued identification and development of product candidates
- **Attractive terms, with potential total deal value of more than $3.1 billion**
  - Sage to receive tiered royalties on sales outside of the United States in the high teens to low twenties percentage if commercialized
  - 50:50 cost and profit sharing within the United States

Sage Therapeutics™ + Biogen®

$1.5B

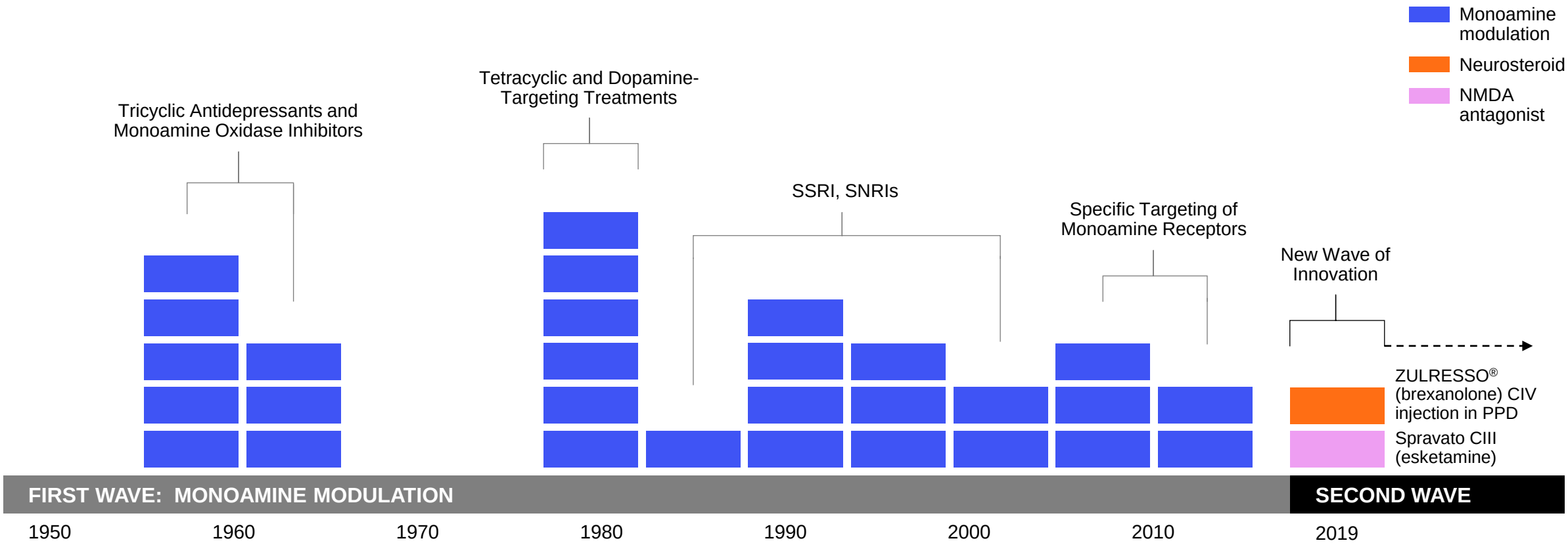
Upfront payment and equity investment

$1.6B

Potential development & commercial milestones

Sage Leading Second Wave of Neuropsych Innovation

First new MOA in 60 years



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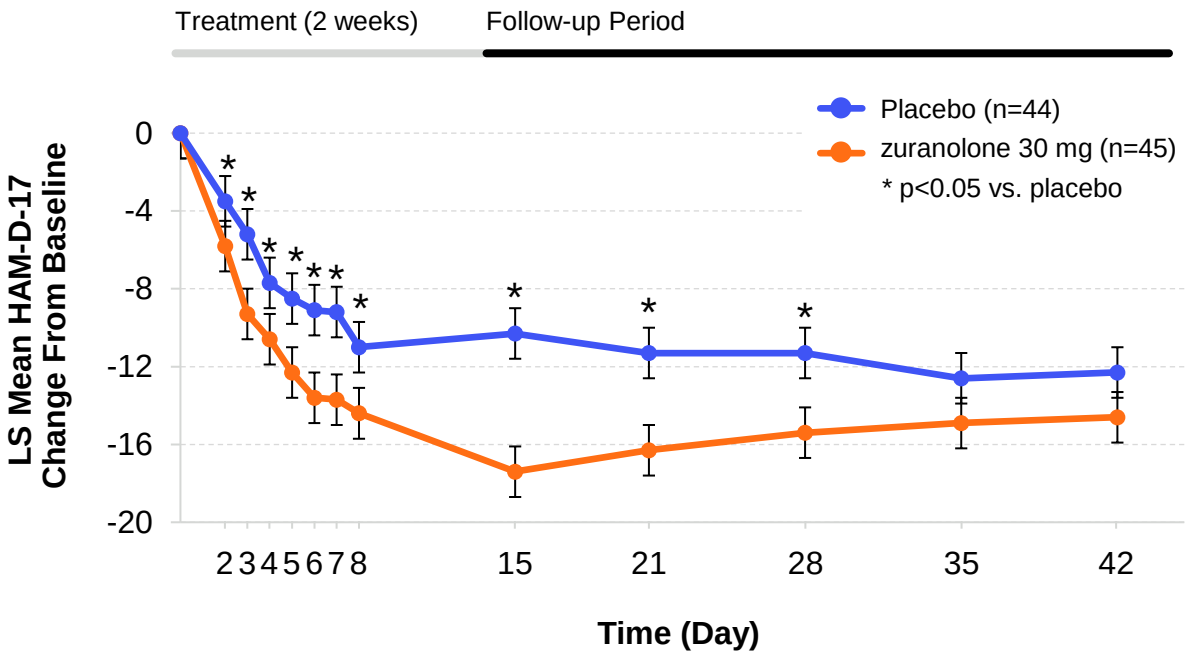
Source: Thomas, D., & Wessel, C. (2017). The State of Innovation in Highly Prevalent Chronic Diseases: Volume I: Depression Therapeutics. BIO.

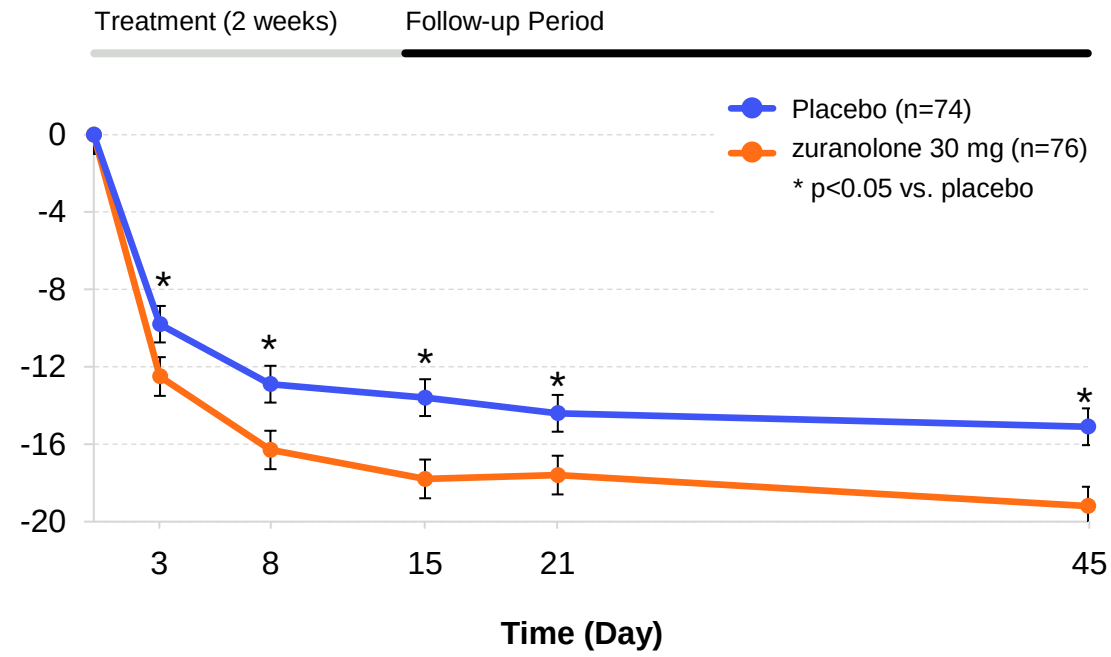
MDD-201 & ROBIN Studies

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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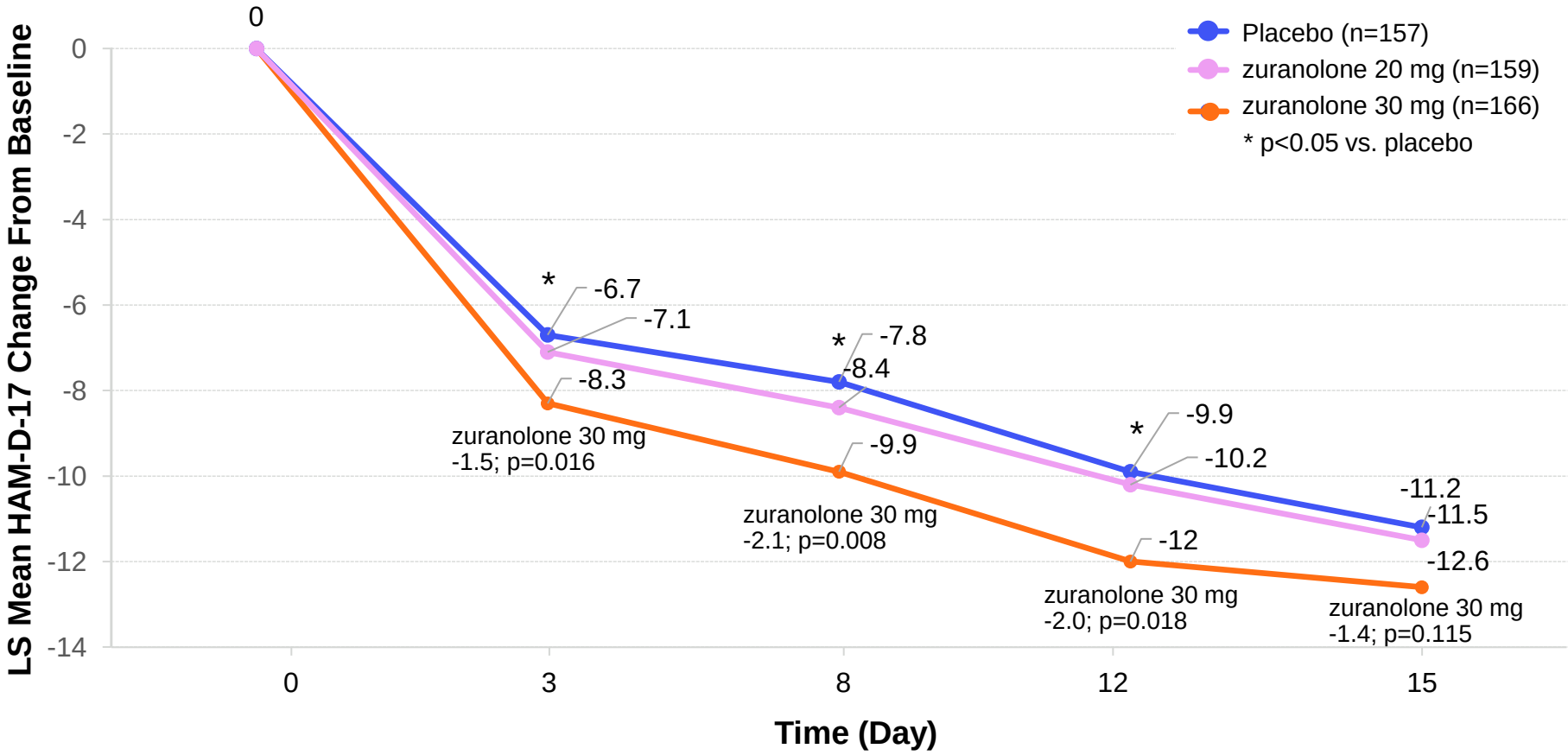
Abbreviations: AEs = adverse events

MOUNTAIN (MDD-301) Study

Displayed 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 although primary endpoint at Day 15 was not met

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Abbreviations: AEs: = adverse events

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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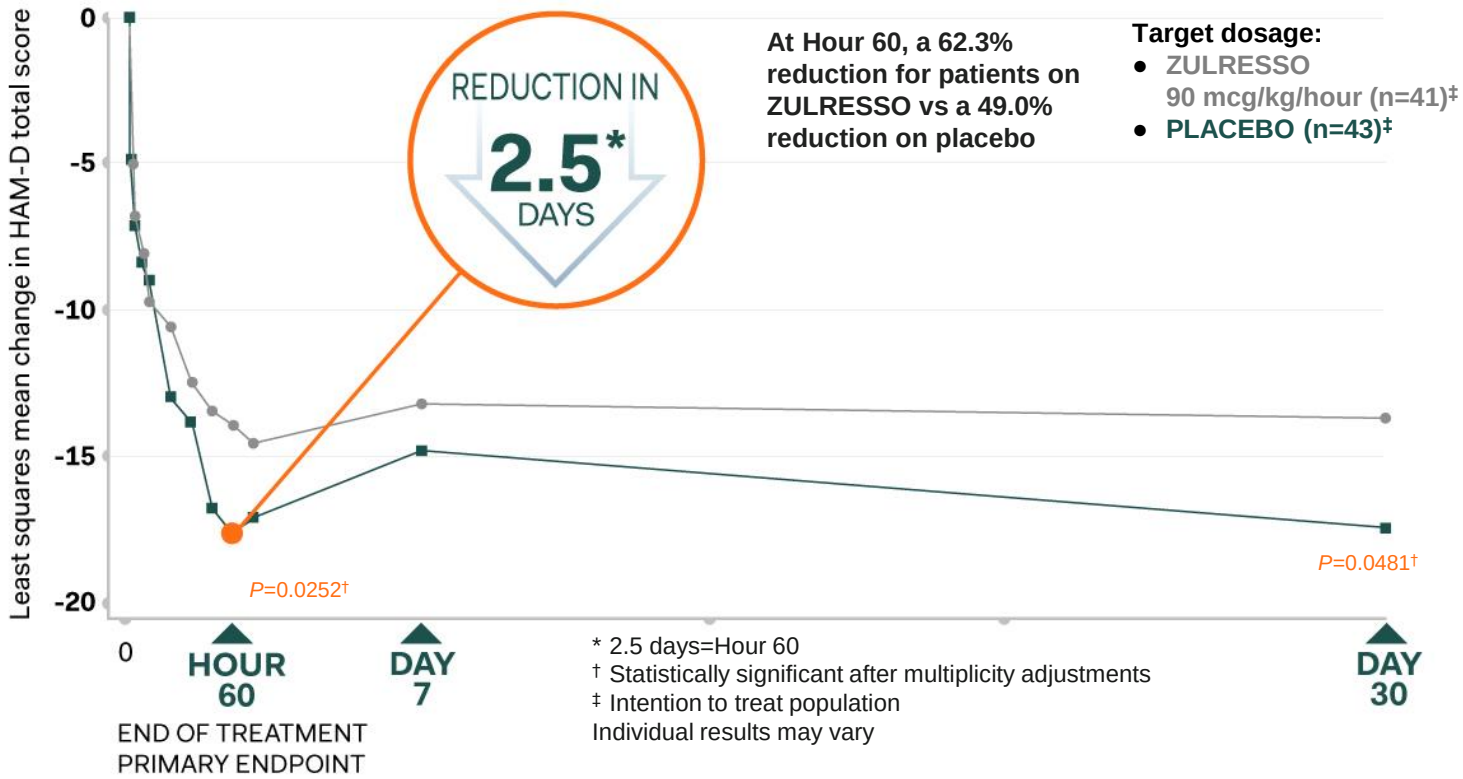
ZULRESSO® (brexanolone) CIV Injection

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

Sage Therapeutics™

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)

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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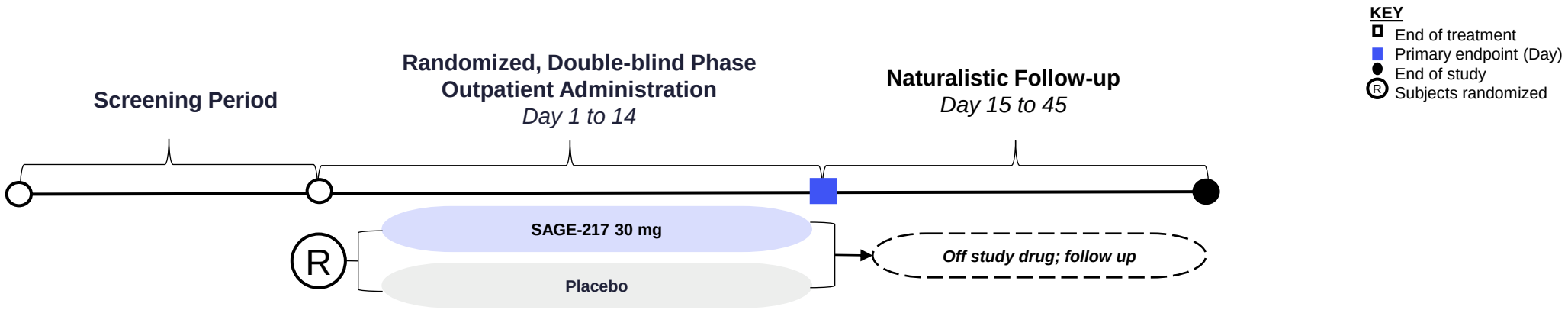
Study Design:

Completed Studies

Completed SAGE-217 Studies

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



STUDY OVERVIEW

Arms	Randomization: 1:1 • SAGE-217 30 mg • 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 • Subject is ≤ six months postpartum • 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
			• Attempted suicide associated with current episode of PPD (Note, suicidal ideation is not an exclusion; other protocol-defined inclusion/exclusion criteria may apply)
			• Medical history of seizures, bipolar disorder, schizophrenia, and/or schizoaffective disorder
				Secondary Endpoints	• Safety and tolerability compared with placebo as assessed by:
					  • Incidence of AEs, vital signs, clinical laboratory evaluations, ECG parameters**
					  • C-SSRS**

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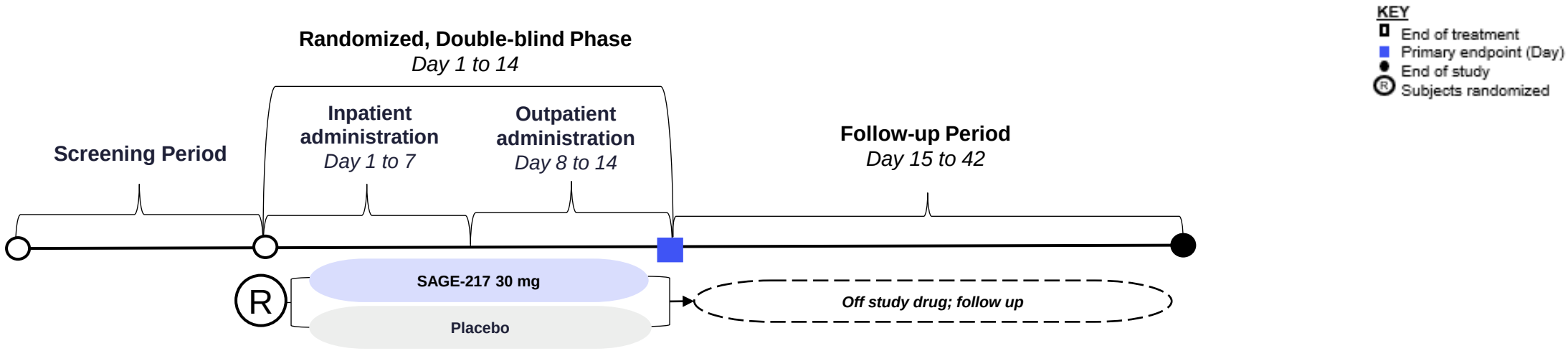
*During double-blind phase; **During double-blind and follow-up periods |NCT02978326. Available from: clinicaltrials.gov [accessed November 2019]

Completed SAGE-217 Studies

Pivotal Ph. 2 in MDD (MDD-201)



STUDY OVERVIEW

Arms	Randomization: 1:1 • SAGE-217 30 mg • 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 • 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	**Secondary Endpoints**	• 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**

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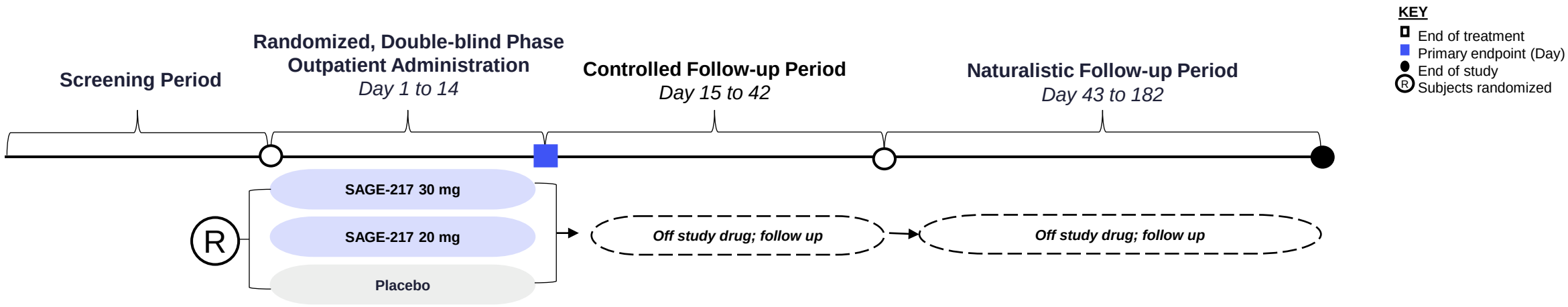
*During double-blind phase; **During double-blind and follow-up periods | NCT03000530. Available from: clinicaltrials.gov [accessed November 2019]

Completed SAGE-217 Studies

Phase 3 MOUNTAIN (MDD-301)



STUDY OVERVIEW

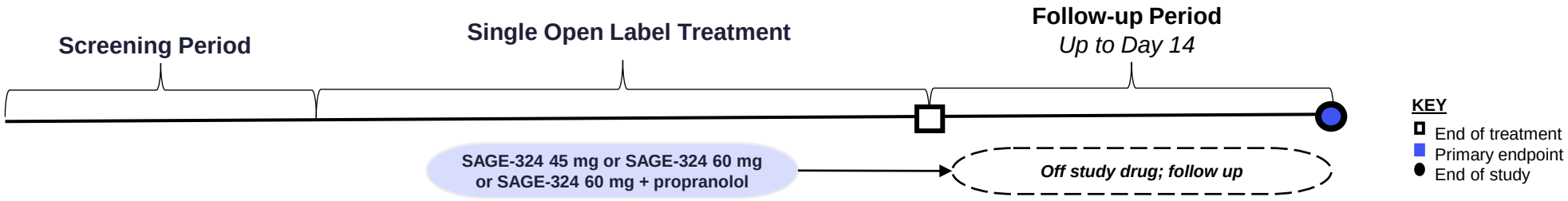
Status	Complete	**Inclusion Criteria**	• Diagnosis of MDD with symptoms that have been present for at least a 4-week period • MADRS total score ≥32 and HAM-D total score ≥22 at screening and Day 1 (prior to dosing)
Indication	MDD		
Phase	Phase 3	**Exclusion Criteria**	• Active psychosis • Attempted suicide associated with the current episode of MDD • Medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder
Start/End Date* *topline data announced	Sep. 2018; Dec. 2019		
Arms	Double-blind, randomized: 1:1:1 • 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** • 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
			  • bilateral upper limb action tremor
			  • at least 3 years duration
			  • with or without tremor in other locations
			  • absence of other neurological signs
			• 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) • Current or recent exposure to tremorgenic drugs or drug withdrawal state • Previous surgery for the treatment of ET
Start/End Date	Aug. 2018 / Dec. 2019		
Cohorts	Open-label study: • SAGE-324 45 mg • SAGE-324 60 mg • 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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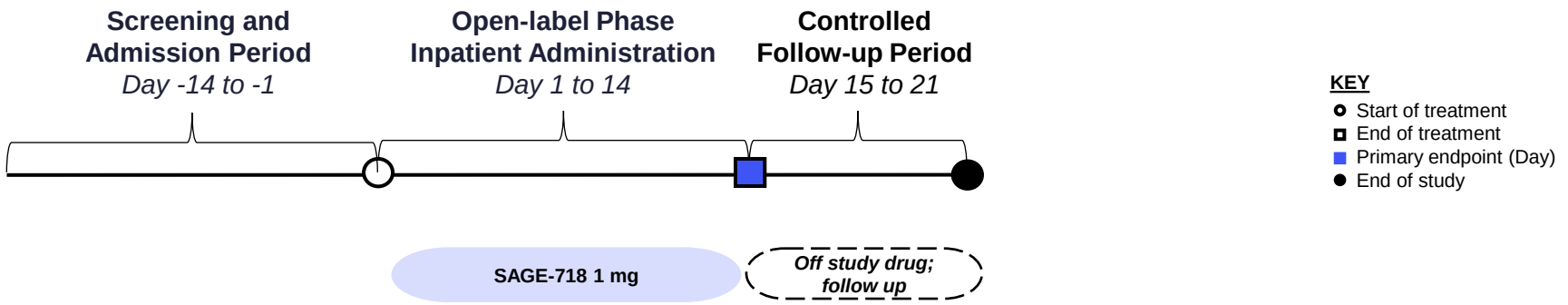
Completed SAGE-718 Study

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) • Total Functional Capacity (TFC) score > 6 • 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 • Change from baseline on a computerized cognitive battery

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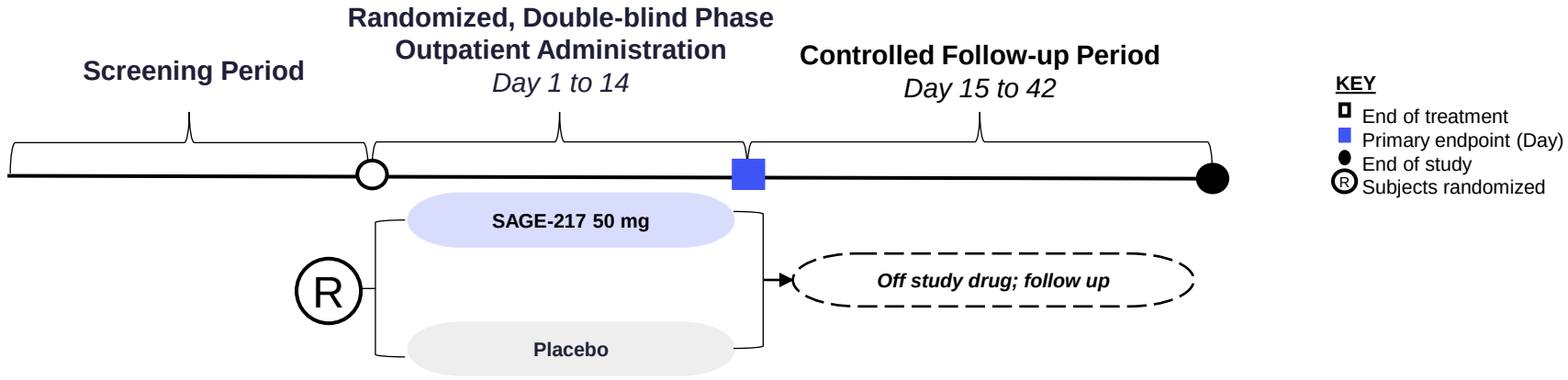
Study Design:

Planned / Ongoing Studies

Zuranolone (SAGE-217) - 50 mg

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



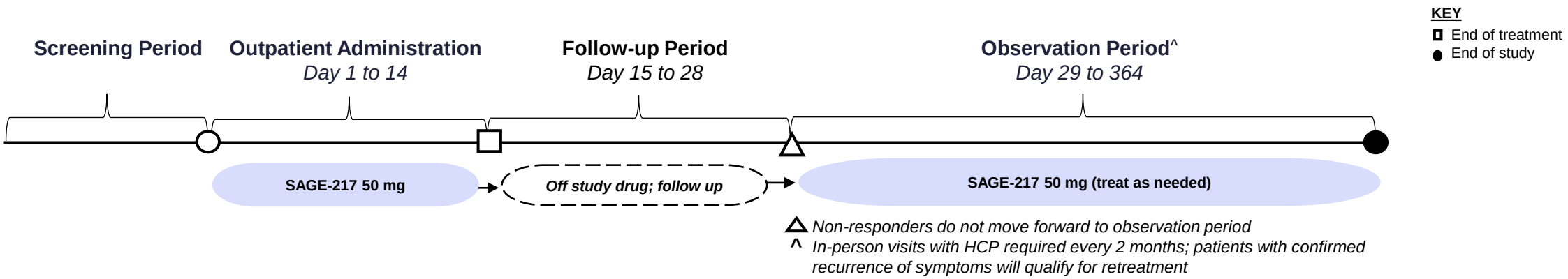
STUDY OVERVIEW

Status	Planned 2020 Initiation	**Inclusion Criteria**	• Diagnosis of MDD with symptoms that have been present for at least a 4-week period • HAM-D total score ≥24 at screening and Day 1 (prior to dosing)
Indication	MDD		
Phase	Phase 3	**Exclusion Criteria**	• Active psychosis • Attempted suicide associated with the current episode of MDD • Medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder
Data Timing	1H21		
Arms	Double-blind, randomized: 1:1 • 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 • 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 • 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	Late 2021	**Exclusion Criteria**	• Attempted suicide associated with the current episode of MDD • Medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder • Subject has had vagus nerve stimulation, electroconvulsive therapy, or has taken ketamine (including esketamine) within the current major depressive episode
Arms	Non-randomized; 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*
			• Response of initial treatment and/or retreatment, as assessed by:
			  • Change from baseline in HAM-D, CGI-S*
			  • 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*
			  • Percent of subjects achieving CGI-I*

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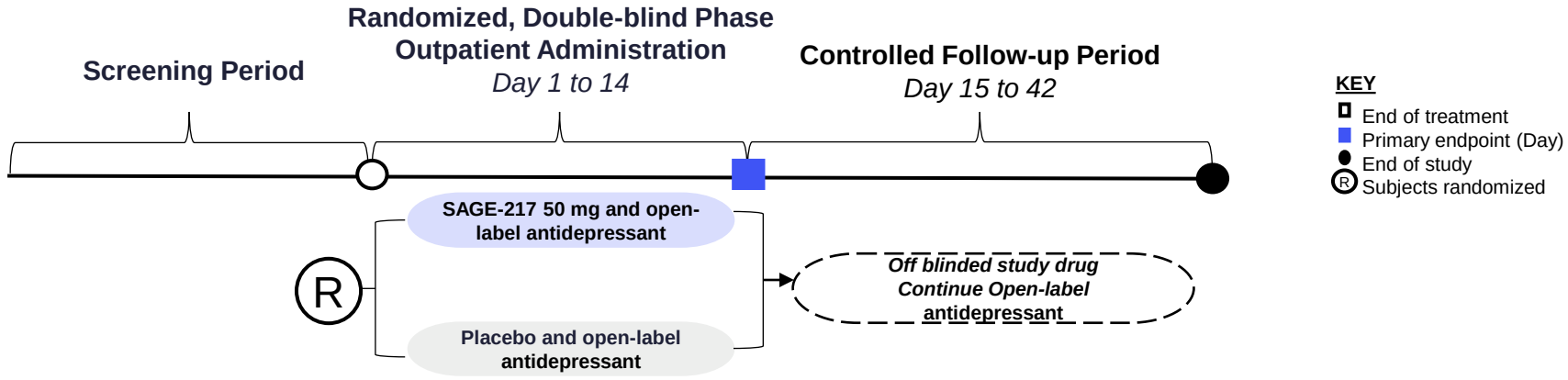
50

*During double-blind and follow-up periods | NCT03864614. Available from: clinicaltrials.gov [accessed November 2019]

Zuranolone (SAGE-217) - 50 mg

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



STUDY OVERVIEW

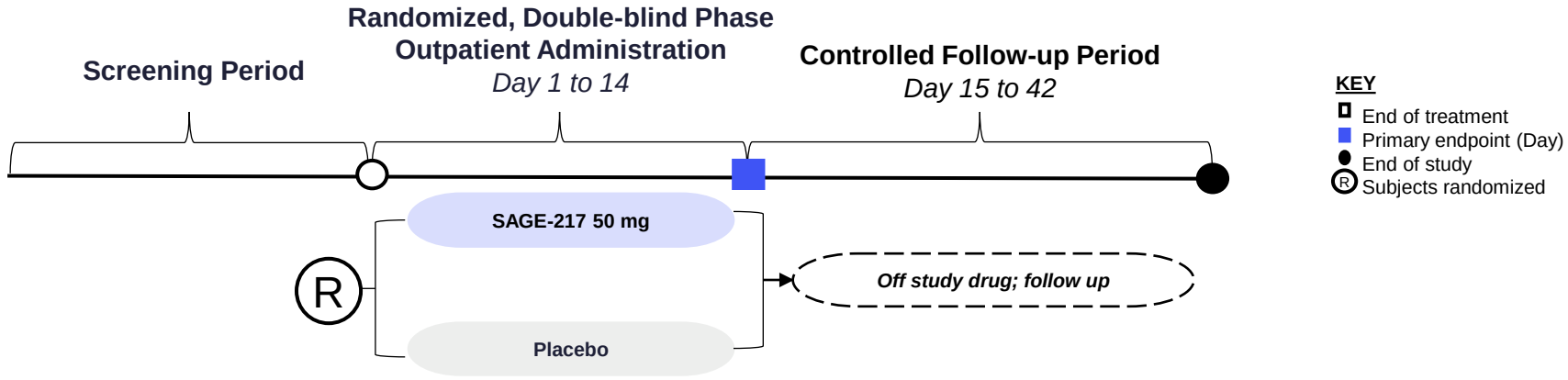
Status	Planned 2020 Initiation	**Inclusion Criteria**	• Diagnosis of MDD with symptoms that have been present for at least a 4-week period • HAM-D total score ≥24 at screening and Day 1 (prior to dosing)
Indication	MDD		
Phase	Phase 3	**Exclusion Criteria**	• Active psychosis • Attempted suicide associated with the current episode of MDD • Medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder
Data Timing	Late 2021		
Arms	Double-blind, randomized: 1:1 • 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 • 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)*



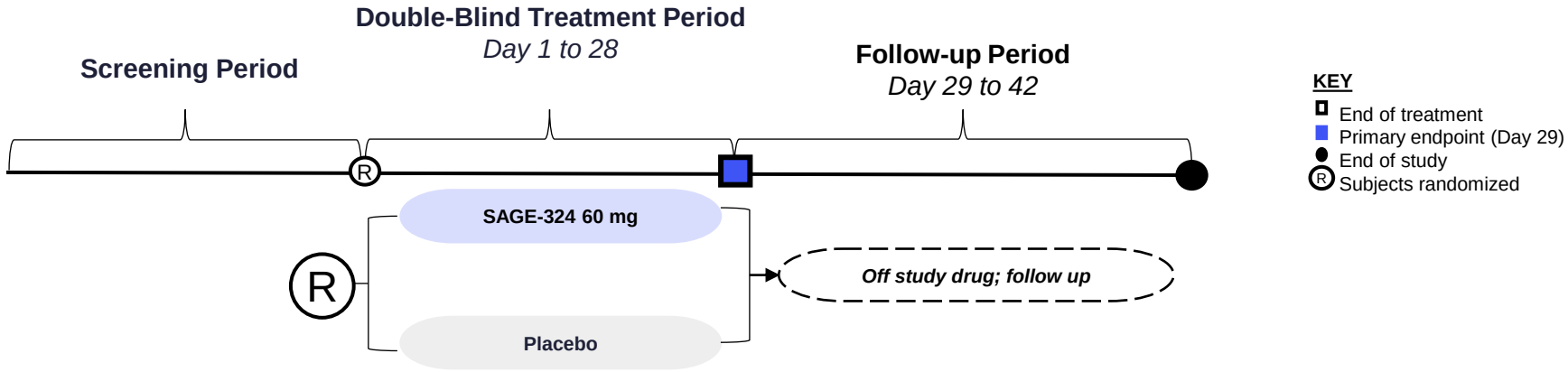
STUDY OVERVIEW

Status	Planned 2020 Initiation	**Inclusion Criteria**	• Diagnosis of MDD with symptoms that have been present for at least a 4-week period • HAM-D total score ≥26 at screening and Day 1 (prior to dosing)
Indication	PPD		
Phase	Phase 3	**Exclusion Criteria**	• Active psychosis • Attempted suicide associated with the current episode of PPD • Medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder
Data Timing	Late 2021		
Arms	Double-blind, randomized: 1:1 • 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 • 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	**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

Indication	Essential Tremor (ET)		
Phase	Phase 2	**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
Data Timing	Early 2021		
Arms	Double-blind, randomized: 1:1 • SAGE-324 60 mg: placebo	**Primary Endpoint**	• Change from baseline in TETRAS performance subscale part 4 upper limb tremor score on Day 29
Dosing Regimen	28 days, once-daily	**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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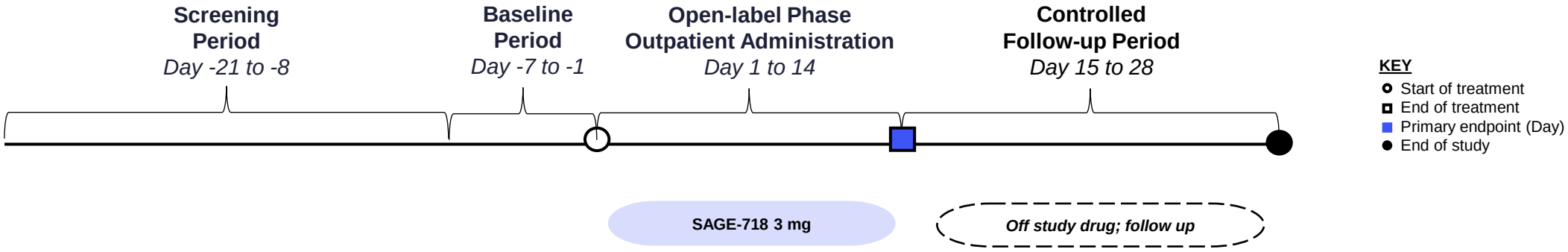
SAGE-718

*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 • Score 20 to 25 (inclusive) on the MoCA at Screening
Indication	PD-MCI		
Phase	Phase 2	**Exclusion Criteria**	• Diagnosis of dementia of any etiology • Experiencing fluctuations in motor and/or non-motor symptoms of Parkinson's disease
Data Timing	Early 2021		
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) • Change from baseline on comprehensive neurocognitive and neuropsychiatric batteries

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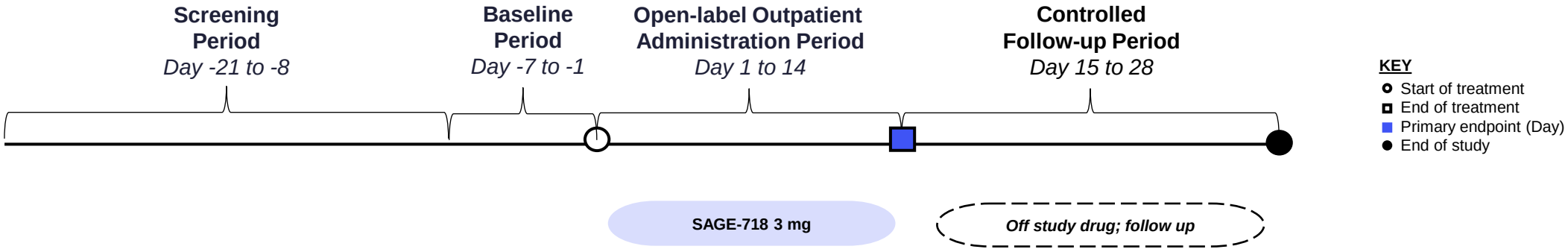
SAGE-718

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 • 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
Data Timing	Late 2021		
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) • Change from baseline on comprehensive neurocognitive and neuropsychiatric batteries

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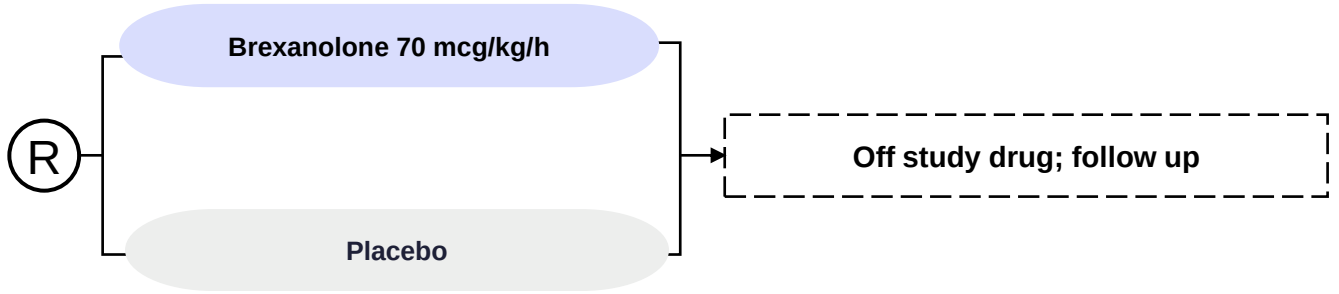
Clinical Study Design – ARDS Due to COVID-19

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 • ARDS • 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 • Brexanolone 70 mcg/kg/h • Placebo	**Secondary Endpoints**	• Treatment-emergent adverse events • All-cause mortality through Day 28
Dosing Regimen	60 Hour Continuous IV Infusion	**Additional Endpoints**	• Respiratory parameters • Change in cytokines and inflammatory markers • Changes in anesthetic dose

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