Sage Therapeutics®

J.P. Morgan Healthcare Conference

January 2023

Safe Harbor Statement

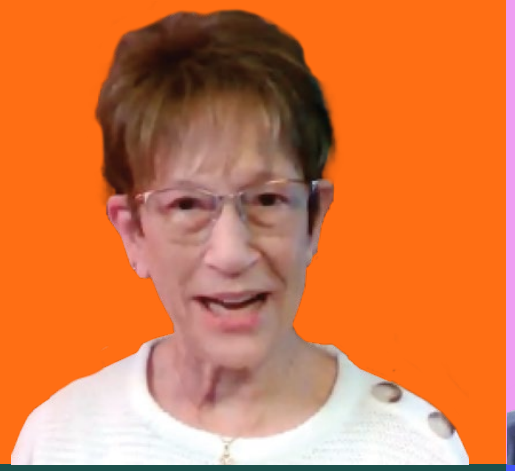
- The slides presented today and the accompanying oral presentations contain forward-looking statements, which may be identified by the use of words such as “may,” “might,” “will,” “should,” “can,”,“expect,” “plan,” “anticipate,” “believe,” “estimate,” “project,” “intend,” “future,” “opportunity”, “goal”, “mission”, “potential,” “target”, or “continue,” and other similar expressions.
- Forward-looking statements in this presentation include statements regarding: our clinical development plans, including expected timelines for activities and our expectations as to potential results; our belief that our NDA for zuranolone will be accepted and the possibility of priority review; the potential for approval and launch of zuranolone and potential timelines; our belief in the potential benefit and profile of zuranolone and in its potential to be successful and to meet an unmet need in the treatment of MDD and PPD; the potential for commercialization of zuranolone and our commercialization plans, including plans to help enable access; our expectations as to the types of MDD patients who may benefit from zuranolone, if approved; the potential for success of our other product candidates in various indications, including the potential profile and benefit of our other product candidates; our estimates as to the number of patients with disorders and diseases of interest to us and that we hope to help and the potential market for our product candidates, if approved; the goals, opportunity, mission and vision for business; and our views with respect our financial strength and potential value creation opportunities.
- 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 FDA may not accept our NDA for zuranolone for review or may accept the filing for review but not grant approval or may grant approval for a narrower indication than we expect or with unexpected limitations. The FDA may ask for additional clinical trials, nonclinical studies or other data in order for us to file for or obtain regulatory approval of zuranolone. The FDA may not grant priority review of our NDA for zuranolone. Our expectations for timing of review of our NDA and of launch of zuranolone, if approved, may not be accurate. The FDA may ultimately decide that the design or results of our clinical trials for our product candidates are not sufficient to successfully file for or obtain regulatory approval.
  - 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. Non-clinical and clinical results from ongoing or future trials may not support further development of the product candidate or filing for or obtaining regulatory approval on the timelines we expect or at all and we may be required to conduct additional clinical trials or nonclinical studies which may not be successful.
  - 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.
  - 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, different frequency or length of dosing or in new indications we are studying or may study in ongoing or planned trials.
  - 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. 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.
  - Even if zuranolone is approved, we may not achieve market acceptance or use of zuranolone in the MDD and PPD patient types we expect and we may not achieve reimbursement of zuranolone at the levels or with the type of access we expect. The benefit and safety profile of zuranolone in clinical practice, if approved, may not meet our expectations. We may not be successful in execution of our planned commercialization activities or we may change our plans. We may never be successful or achieve our goals with respect to commercialization of zuranolone, if approved.
  - Even if zuranolone or our other product candidates are successfully developed and approved, the number of patients with the diseases or disorders our products treat or the subset of such patients we believe will use our products, the need for new treatment options, and the actual market for such products may be smaller than our current estimates.
  - The anticipated benefits of our collaborations, including our collaboration with Biogen, may never be achieved. The need to align with our collaborators may hamper or delay our development and commercialization efforts or increase our costs; our business may be adversely affected and our costs may increase if any of our key collaborators fails to perform its obligations or terminates our collaboration.
  - We may not be able to obtain and maintain adequate intellectual property protection or other forms of data and marketing exclusivity for our products, or to defend our patent portfolio against challenges from third parties.
  - We may face competition from others developing products or with approved products for similar uses as those for which our product candidates are being developed.
  - Our operating expenses may be higher than forecasted, our revenues may be lower than we expect, or we may face unexpected expenditures, which could cause us to change our plans. We may need or choose to raise additional funding, which may not be available on acceptable terms, or at all.
  - We may not be able to establish and maintain key business relationships with third parties on acceptable terms or we may encounter problems with the performance of such third parties.
  - We may encounter technical and other unexpected hurdles in the manufacture, development or commercialization 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

The time is now…

Kay
Postpartum Depression (PPD)

Lynn
Essential Tremor (ET)



Seth
Huntington's Disease (HD)

Sheante
Major Depressive Disorder (MDD)

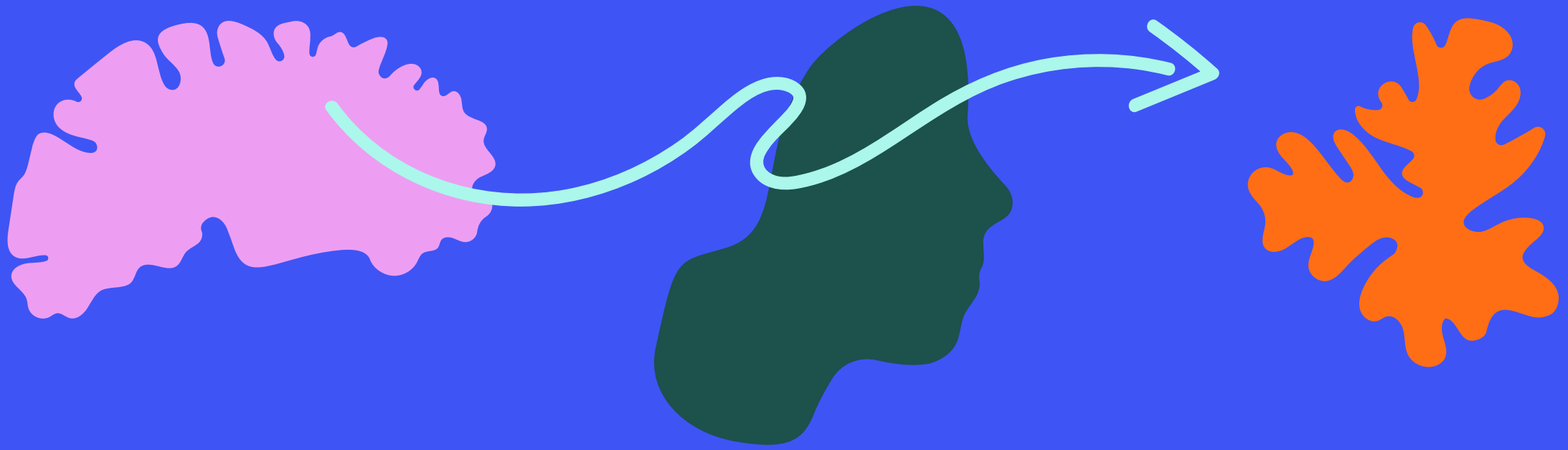
Dan
Parkinson's Disease (PD)

Kirsten
Alzheimer's Disease (AD)

Brain health is *fundamental to good health*

Sage Therapeutics

Building impact and scale



Millions of people have been waiting **decades for new treatment options**

Patients, providers, and society can and **must be better served**

Relentless focus on developing **new and effective treatments to address brain health disorders**

The time is now…

Challenge scientific convention

Starting with our work on GABA and NMDA, we are pursuing breakthroughs that have the potential to advance the treatment of a wide range of brain health disorders.

Building a business for the future

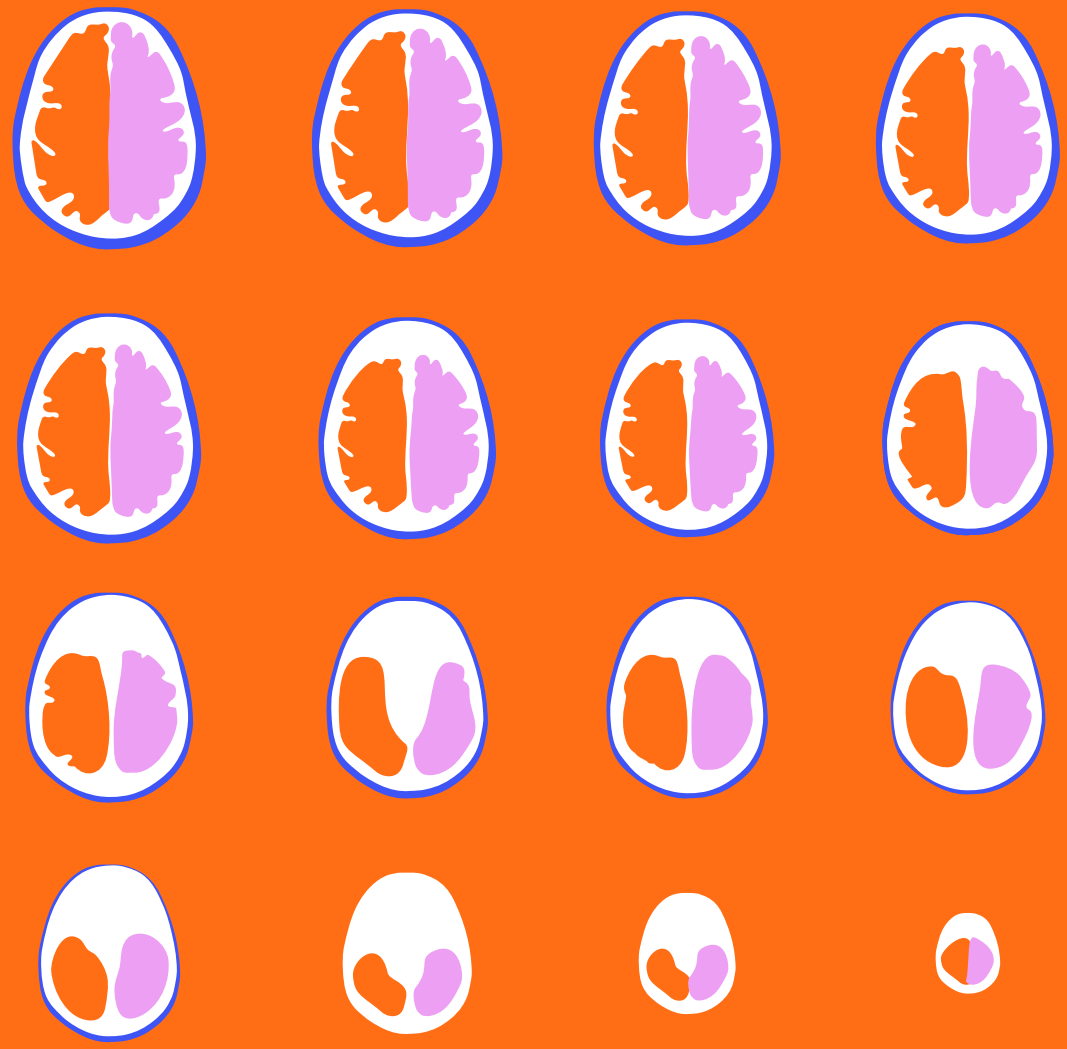
Rich innovative pipeline/product engine

Deep expertise in brain circuitry

Significant potential patient impact

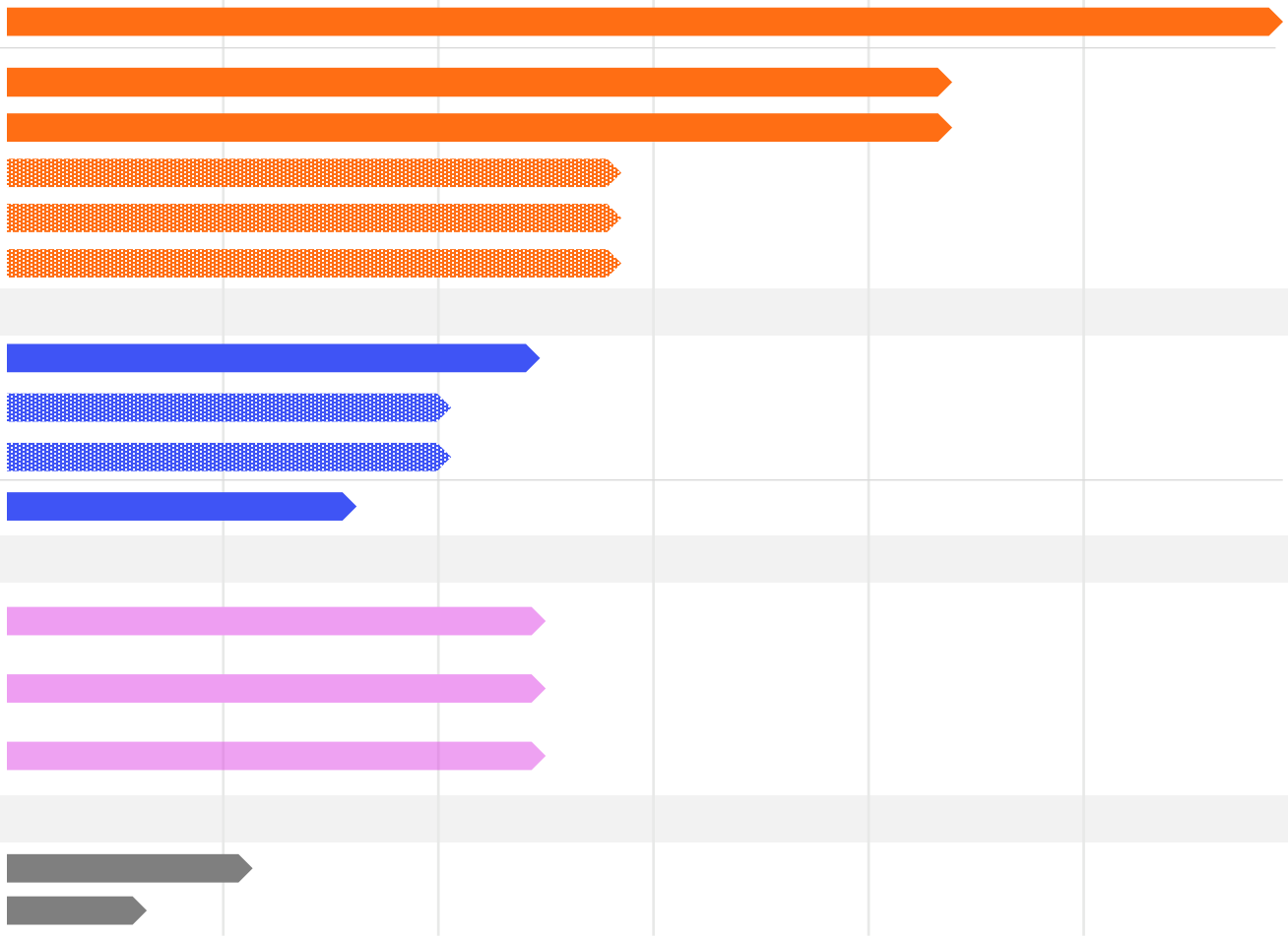
Strong cash position to fuel growth

Exciting business momentum into 2023



Sage has a leading brain health portfolio

COMPOUND	PARTNER	INDICATIONS
DEPRESSION		
ZULRESSO® (brexanolone) CIV injection		Postpartum Depression
Zuranolone (SAGE-217)	Biogen, SHIONOGI	Major Depressive Disorder
		Postpartum Depression
		Treatment Resistant Depression
		Generalized Anxiety Disorder
		Bipolar Depression
NEUROLOGY		
SAGE-324	Biogen	Essential Tremor
		Epileptiform Disorders
		Parkinson's Disease
SAGE-689		Acute GABA Hypofunction
NEUROPSYCHIATRY		
SAGE-718		Huntington's Disease Cognitive Dysfunction
		Parkinson's Disease Cognitive Dysfunction
		Alzheimer's Disease Mild Cognitive Impairment and Mild Dementia
EARLY DEVELOPMENT		
SAGE-319		GABA Hypofunction
SAGE-421		NMDA Hypofunction



Sage Therapeutics

Light shades indicate trials in the planning or evaluation stage

Significant unmet needs remain in the treatment of depression

Unmet Needs

In a survey of MDD patients (n=583) conducted by Sage, 75% of MDD patients asked about the impact of switching medications reported being frustrated or feeling that no medication was going to work for them[1]

1

STAR*D Analysis shows that patients who achieve later remission have a 1.5 times higher risk of relapse than those who remit early[1]

2

The economic burden of MDD in the United States is an estimated $326 billion in 2018[2]

3

Sage Therapeutics

MDD = major depressive disorder

1. Sage Therapeutics. Data on file. 2. Greenberg PE, et al. PharmacoEconomics. 2021; 39: 653-665.

Zuranolone clinical data supports its potential to fulfill unmet needs for people with MDD and PPD

Rapid & Sustained

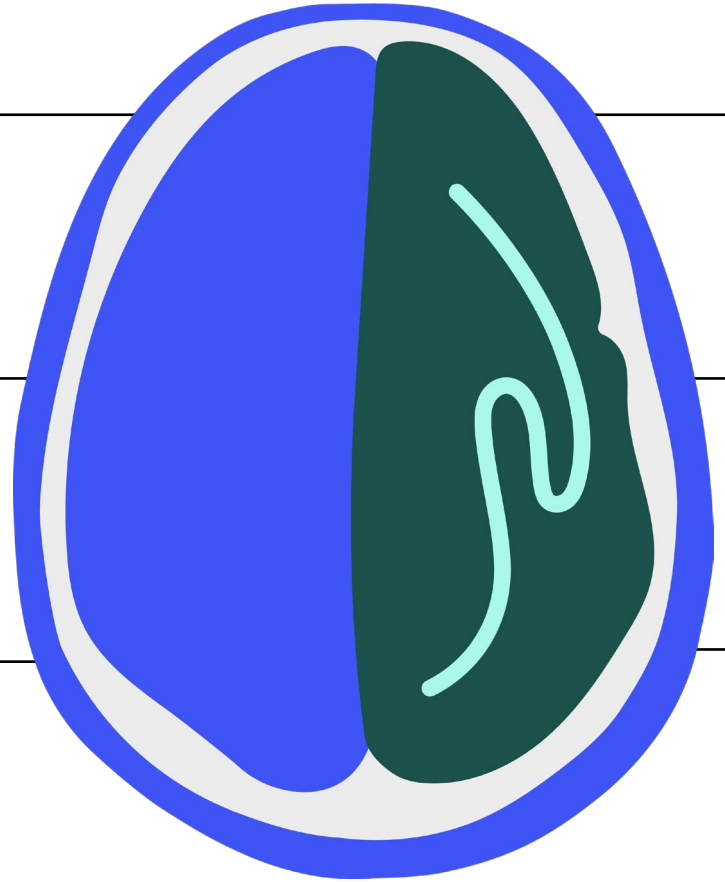
- Rapid symptom reduction observed
- Sustained effects lasted beyond completion of treatment

Well-Tolerated

- Well-tolerated profile*
- Differentiated side effect profile with no evidence of increased sexual dysfunction, weight gain or sleep disruption

Improved Feel/Functioning

- Improvements seen across domains of quality of life
- Measured benefits that patients are looking for from depression treatment



Short Course

- As-needed oral therapy
- 2-week treatment course

Novel MOA

- Selectively modulates $GABA_AR$
- May help neuronal networks rebalance[1]

Flexible Approach

- Improvement seen in depressive symptoms in MDD/PPD patients when used as mono or adjunctive therapy
- Improvements seen in MDD/PPD patients with or without elevated anxiety

*Zuranolone was generally well-tolerated across clinical studies. The most common adverse events associated with zuranolone included headache, somnolence, dizziness and sedation.

Profile based on data demonstrated in clinical studies with zuranolone to date

Note: Success of zuranolone and the product profile depend on the clinical development program and regulatory approval.

[1]Antonoudiou, P. et al. Allopregnanolone mediates affective switching through modulation of oscillatory states in the basolateral amygdala. *Biological Psychiatry*, 2021.2003.2008.434156, doi:10.1016/j.biopsych.2021.07.017 (2021).

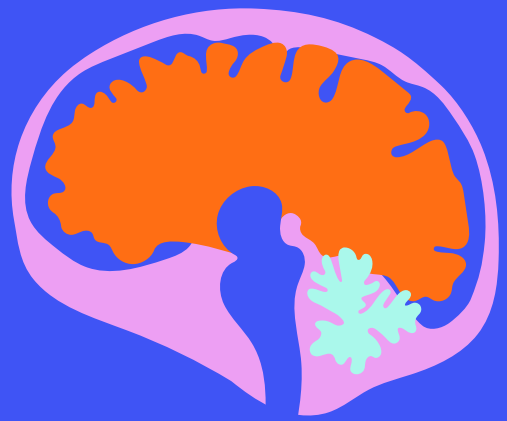
MDD = major depressive disorder, PPD = postpartum depression

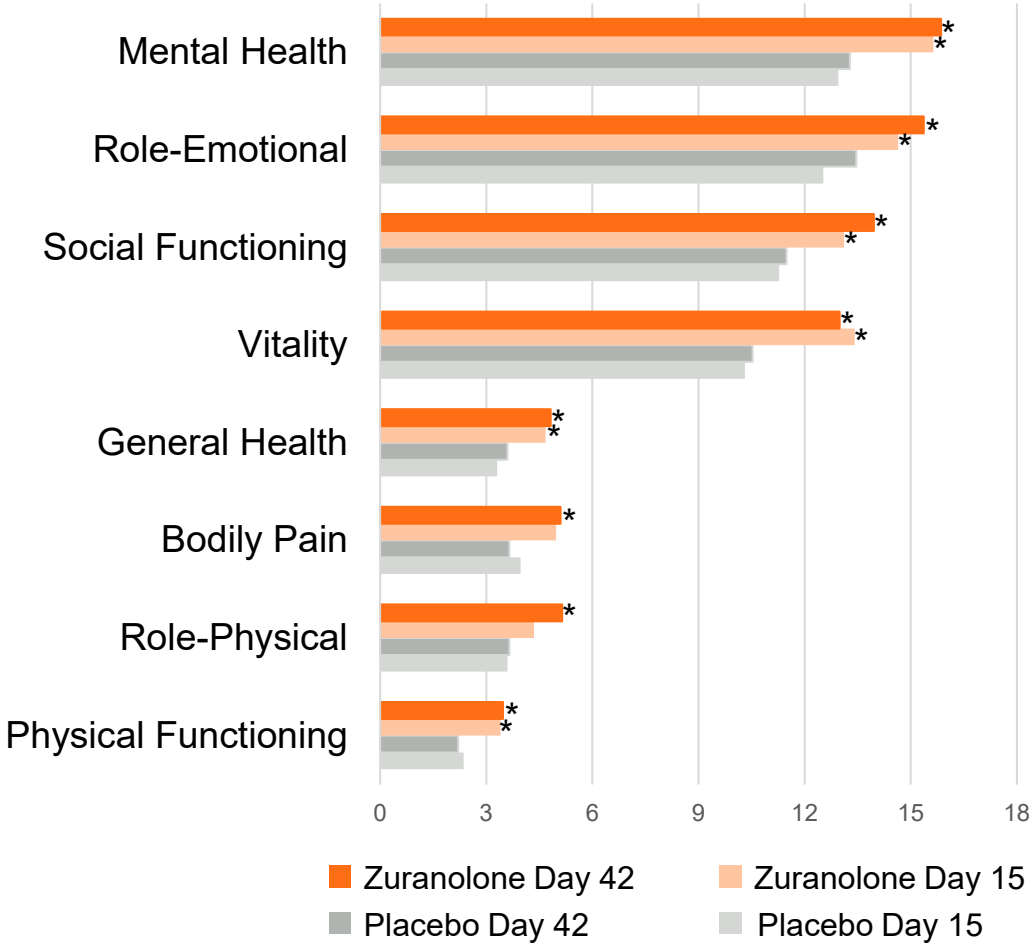
Zuranolone is being developed in collaboration with Biogen.

Sage Therapeutics®

In an integrated analysis of zuranolone data, patients reported overall improvement in functioning and well-being†

Clinically meaningful improvements were observed *across mental health, physical and general health domains of SF-36*





*LSM treatment difference p-value <0.05 (nominal); †Integrated analyses combine doses from the ROBIN Study, MDD-201B Study, MOUNTAIN Study (≥24 HAMD-17 subgroup), and WATERFALL Study. ‡For the ROBIN study, data were collected at Day 45.; SF-36 = 36-Item Short Form Health Survey (version 2).

Zuranolone is being developed in collaboration with Biogen.

Selected responder interviews from SHORELINE Study in MDD

Examples of quotes from surveyed patients who responded to initial treatment cycle of 50 mg zuranolone in the open-label SHORELINE Study (n=32)

"It was really impressive that the results happened so quickly, and it was so dramatic. It wasn't just a slight improvement, it was night and day. **It was a 180 degree turn from how I'd been feeling even just the day before**."

Rapid Onset

A substantial majority of interviewed patients noticed improvements within the first week

"...almost like an afterglow of the two week course of treatment, that then it was just working for several months. **I didn't have to think about it constantly. I didn't have to take medication...I wasn't having to think about my depression and try to manage it."**

Durability

Most interviewed patients reported being satisfied with duration of improvements

"I felt better both times… I started feeling better right away…and I wasn't as bad when I took it the second time as I had been before the study."

Retreatment

A significant majority of interviewed patients who received retreatment reported feeling fine, positive, or neutral about needing to be retreated

"Very satisfied because it's helping me. I feel better about myself now than I did when I first started. I know it's good…I'm doing more than I used to. I'm getting up. I'm going to church. Before, I wouldn't be anywhere, I wouldn't go outside, I would just look outside the door. It has helped me."

Satisfaction

All interviewed patients reported being moderately, quite, or very satisfied with zuranolone

Among patients treated in the ongoing open-label Phase 3 SHORELINE Study, the most common TEAEs (>5%) observed in the 30 and 50 mg cohorts were headache, somnolence, dizziness, and sedation.
Patient experiences are provided solely to help illustrate the data collected from the SHORELINE Study interviews. Patient experiences in the SHORELINE Study differed patient-to-patient. Results of the survey are not intended to make claims about zuranolone's potential benefit. Survey information does not represent all patients who took zuranolone.
Interviews conducted with patients who responded to the first 50 mg zuranolone treatment cycle and had been participants in the SHORELINE Study for at least six months. Interviews were conducted at various timepoints for each patient. Based on SHORELINE Study design, patients were allowed to be on background therapy. Sample size of interviewed patients n = 32.
MDD = major depressive disorder
Zuranolone is being developed in collaboration with Biogen.

Sage Therapeutics®

Goal of the planned zuranolone launch strategy is to transform the way MDD and PPD are treated

MDD – Partial Response

MDD with Elevated Anxiety

MDD – Adherence Challenged

PPD

If zuranolone is approved, plan to focus on: Priority MDD and PPD patient segments

Target High Volume HCPs

- Psychiatrists
- NPs / PAs
- PCPs
- OBGYNs

Collaborate with Payers

Lead with Value

Sage Therapeutics®

Sage and Biogen Zuranolone Webcast [December 6, 2022]. Accessible via: https://investor.sagerx.com/events/event-details/sage-therapeutics-and-biogen-webcast-discuss-potential-commercialization-plans

MDD = major depressive disorder, PPD = postpartum depression, NP = nurse practitioner, PA = physician assistant, PCP = primary care provider

Zuranolone is being developed in collaboration with Biogen.

Cognitive impairment is prevalent and impacts people across the lifespan

Executive Function

Planning, decision-making, working memory, multitasking, flexibility

Learning & Memory

Recall, recognition. long-term memory, implicit learning

Attention

Sustained attention, divided attention, selective attention, processing speed

Language

Object naming, word finding, fluency, grammar and syntax, receptive language

Visuospatial

Visual perception. Visuo-constructional reasoning, perceptual-motor coordination

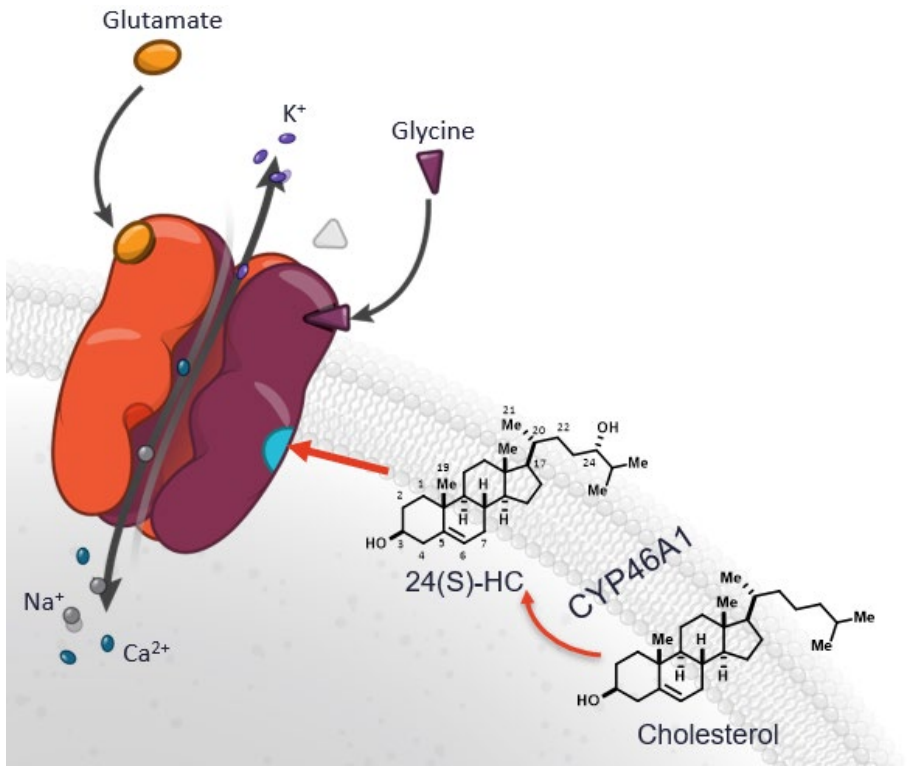
DAILY LIFE

Sage Therapeutics®

Sources: SSM Popul Health. 2020 Aug; 11: 100577. Published online 2020 Mar 31. doi: 10.1016/j.ssmph.2020.100577
https://altoida.com/blog/defining-the-6-key-domains-of-cognitive-function/

Sage's first-in-class NMDA receptor PAM

Novel starting point for understanding NMDA receptor modulation



Emerging Science Drives New Thinking

- The neuroactive steroid, 24S-hydroxycholesterol (24S-HC), is an endogenous modulator of NMDA receptors
- NMDA receptors play a major role in excitatory transmission in the brain and influence cognition and other key brain functions
- NMDA receptor hypofunction has been implicated in cognitive impairment associated with disorders such as Huntington's disease, Parkinson's disease and Alzheimer's disease

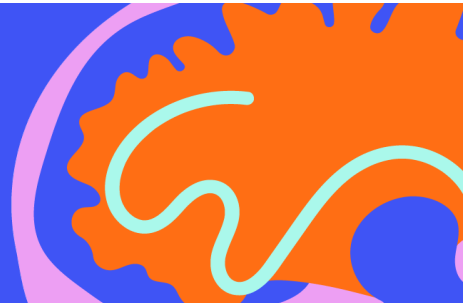
SAGE-718: NMDA Positive Allosteric Modulator (PAM)

- SAGE-718 is a novel, positive allosteric modulator derived from our pharmacological understanding of 24S-HC
- SAGE-718 is believed to bind to a novel neurosteroid site on the NMDA receptor
- SAGE-718 has the potential to restore NMDA activity and improve cognitive functioning

Sage Therapeutics

Globally, disorders involving cognitive impairment continue to increase

Cognitive impairment has devastating impacts on *patients, families, and society*



~188K

Huntington's Disease Global Prevalence[1]

Cognitive Impairment in HD can occur up to 15 years before motor manifestation & is highly associated with overall functional decline

~8.8M

Parkinson's Disease Global Prevalence[2]

Mild cognitive impairment (MCI) is diagnosed in nearly half of people with PD and causes poorer treatment outcomes, greater medical costs, and caregiver distress

~134M

Alzheimer's Disease Global Prevalence[3]

Up to 50% of people with MCI due to AD progress to Alzheimer's dementia within 5-10 years

Sage Therapeutics®

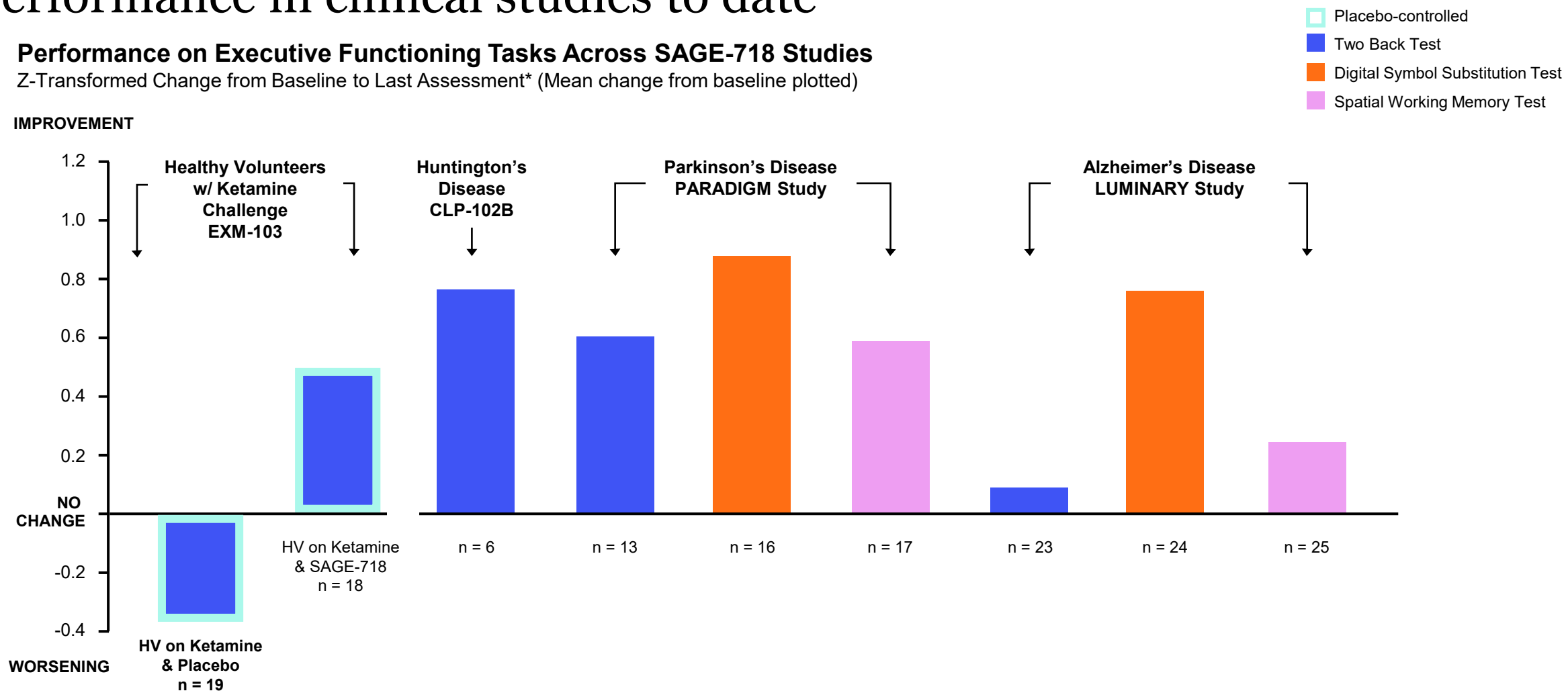
HD = Huntington's disease, PD = Parkinson's disease, AD = Alzheimer's disease

1. Pringsheim T, Wiltshire K, Day L, Dykeman J, Steeves T, Jette N. The incidence and prevalence of Huntington's disease: a systematic review and meta-analysis. Mov Disord. 2012 Aug;27(9):1083-91. doi: 10.1002/mds.25075. Epub 2012 Jun 12. PMID: 22692795. 2. Sage Therapeutics, Inc. Data on file. 3. Sage Therapeutics, Inc. Data on file.

SAGE-718 has demonstrated consistent beneficial effects on cognitive performance in clinical studies to date

Performance on Executive Functioning Tasks Across SAGE-718 Studies

Z-Transformed Change from Baseline to Last Assessment* (Mean change from baseline plotted)



HV = healthy volunteers

SAGE-718 clinical development program in Huntington's disease

PERSPECTIVE PROGRAM

Huntington's Disease

FDA Fast-track Designation

DIMENSION (CIH-201) | 3-month study

- Description: Robust RCT in patients with HD cognitive impairment, designed to evaluate efficacy
- Objective: Demonstrate difference on cognitive performance between drug and placebo at month 3
- Target enrollment: 178

ENROLLING

SURVEYOR (CIH-202) | 1 month study

- Description: Placebo-controlled RCT to demonstrate the clinical meaningfulness of improving cognition in HD
- Objective: Generate evidence linking change in cognitive performance to real-world patient functioning, benchmarked against performance of healthy volunteers
- Target enrollment: 40 people with HD, 40 healthy volunteers (assessment-only HV arm)

ENROLLING

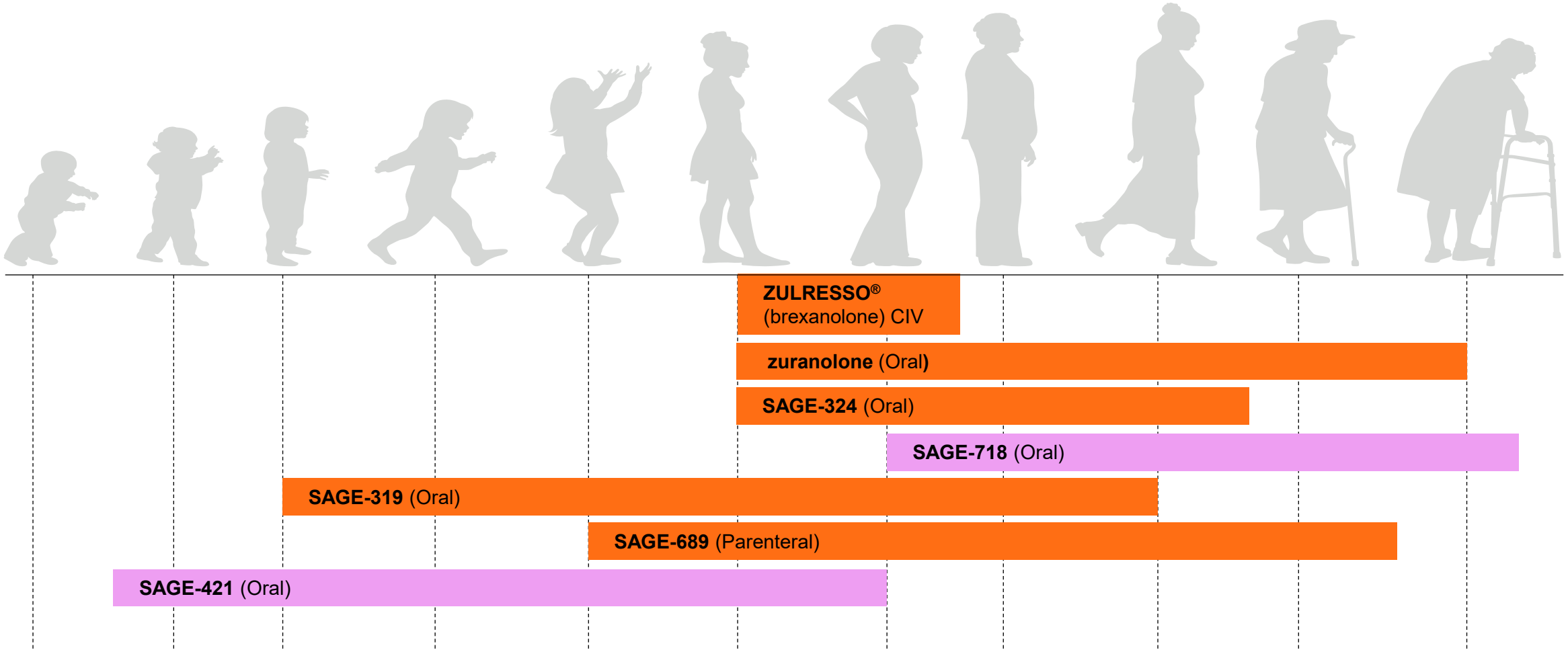
PURVIEW (CIH-301) | 13-month study

- Description: Open-label safety study, enrolling participants from DIMENSION, SURVEYOR, and an additional de novo cohort
- Objective: Designed to evaluate the long-term safety profile and benchmark performance against HD natural history studies
- Target enrollment: 300

ENROLLING

Sage Therapeutics

Sage's robust portfolio features NCEs with differentiated target profiles that may be suited for study across the lifespan



Sage Therapeutics

Anticipated 2023 Milestones

	Early	Mid	Late	*Early:Q1-Q2; Mid:Q2-Q3; Late: Q3-Q4
DEPRESSION				
Zuranolone (SAGE-217)	●			FDA acceptance of rolling NDA submission for zuranolone in MDD and PPD
		●		Present additional data from SHORELINE Study
			●	PDUFA date for zuranolone in MDD and PPD, if accepted for review by the FDA
			●	Commercial availability of zuranolone in MDD and PPD, if priority review is granted and zuranolone is approved
			●	Initiate a lifecycle innovation study with zuranolone
	●	●	●	Present additional analyses of data from LANDSCAPE and NEST clinical programs, including health economics and patient reported outcomes
NEUROLOGY				
SAGE-324			●	Complete enrollment in Phase 2b KINETIC 2 Study
	●	●	●	Present additional analyses of data from clinical development program as well as disease state and burden of disease research in ET
NEUROPSYCHIATRY				
SAGE-718	●	●	●	Progress recruitment in the ongoing DIMENSION, SURVEYOR, PURVIEW, PRECEDENT, and LIGHTWAVE Studies
	●	●	●	Present additional analyses of data from clinical development program as well as disease state and burden of disease research in HD, PD and AD
ADDITIONAL CLINICAL PROGRAMS & MILESTONES				
Additional Pipeline Programs			●	Provide update on next steps for pipeline programs (e.g., SAGE-319)
Cash Balance	●	●	●	Maintain strong balance sheet

Sage Therapeutics®

MDD = major depressive disorder, PPD = postpartum depression, ET = essential tremor, HD = Huntington's disease, PD = Parkinson's disease, AD = Alzheimer's disease

The time is now…

Kay
Postpartum Depression (PPD)

Lynn
Essential Tremor (ET)

Seth
Huntington's Disease (HD)

Sheante
Major Depressive Disorder (MDD)

Dan
Parkinson's Disease (PD)

Kirsten
Alzheimer's Disease (AD)

Brain health is *fundamental to good health*

Sage Therapeutics

Seeing the brain differently *makes a world of difference*

Sage Therapeutics®