



Investor Presentation

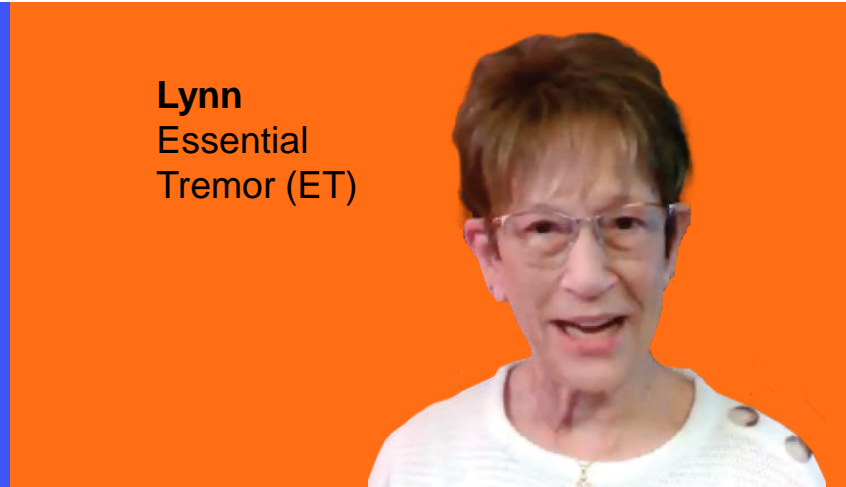
May 2023



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: 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 clinical development plans, including expected timelines for activities and our expectations as to potential results; 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; our expectations with respect to cash, expenses and the potential receipt of milestone payments; and our views with respect to 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 grant approval of our NDA for zuranolone in MDD and PPD or may grant approval for a narrower indication than we expect or with unexpected limitations or restrictions. The FDA may ask for additional clinical trials, nonclinical studies or other data in order for us to obtain regulatory approval of zuranolone or may find other deficiencies in our development program, data, processes, or manufacturing sites that causes the FDA not to approve our NDA. Our expectations for timing of review of our NDA and of launch of zuranolone, if approved, may not be accurate.
 - 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, including market access 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 and we may face unexpected expenses which could cause us to change our plans. Our revenues may be lower than we expect, including if we do not receive approval of our NDA for zuranolone in MDD and PPD or if our launch of zuranolone, if approved, is not as successful as we expect. We may not achieve expected milestones that trigger cash payments on the timing we expect, or at all. For these and other reasons, our expectations with respect to cash, expenses and our financial strength may not prove to be accurate. 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.

The time is now...



Brain health is *fundamental to good health*

Building a business for the future

Deep Expertise in brain circuitry

Rich Innovative pipeline

- First and only product approved specifically for postpartum depression
- 3 late-stage programs
- 6 NCE development programs across 11+ potential indications
- Strong intellectual property strategy

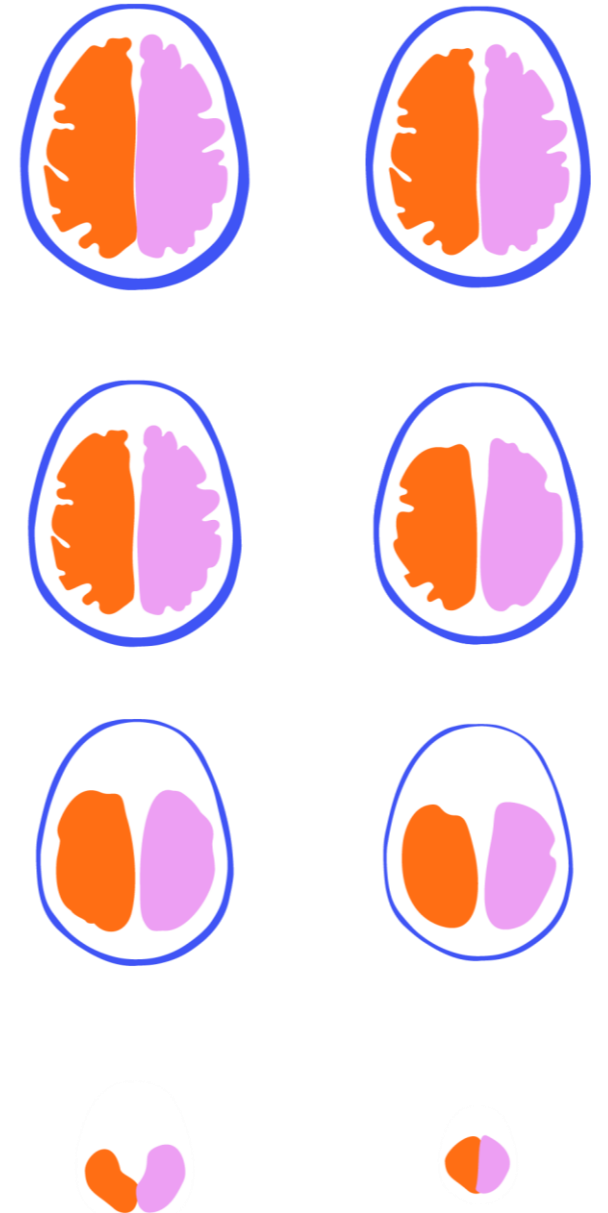
Significant potential patient impact

- Potential to impact an estimated >450M patients globally




Strong cash position to fuel growth

- \$1.1B (as of 3/31/23) and collaborations to fund efforts to accelerate and advance medicines

Exciting business momentum into 2023



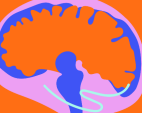
Sage has a leading brain health portfolio

COMPOUND	PARTNER	INDICATIONS	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3	REGISTRATION	MARKETED
DEPRESSION								
ZULRESSO® (brexanolone) CIV injection		Postpartum Depression	[Progress bar: Preclinical to Marketed]					
Zuranolone (SAGE-217)	 	Major Depressive Disorder	[Progress bar: Preclinical to Phase 3]					
		Postpartum Depression	[Progress bar: Preclinical to Phase 3]					
		Treatment Resistant Depression	[Progress bar: Preclinical to Phase 2]					
		Generalized Anxiety Disorder	[Progress bar: Preclinical to Phase 2]					
		Bipolar Depression	[Progress bar: Preclinical to Phase 2]					
NEUROLOGY								
SAGE-324		Essential Tremor	[Progress bar: Preclinical to Phase 1]					
		Epileptiform Disorders	[Progress bar: Preclinical to Phase 1]					
		Parkinson's Disease	[Progress bar: Preclinical to Phase 1]					
SAGE-689		Acute GABA Hypofunction	[Progress bar: Preclinical to Phase 1]					
NEUROPSYCHIATRY								
SAGE-718		Huntington's Disease Cognitive Dysfunction	[Progress bar: Preclinical to Phase 1]					
		Parkinson's Disease Cognitive Dysfunction	[Progress bar: Preclinical to Phase 1]					
		Alzheimer's Disease Mild Cognitive Impairment and Mild Dementia	[Progress bar: Preclinical to Phase 1]					
EARLY DEVELOPMENT								
SAGE-319		GABA Hypofunction	[Progress bar: Preclinical to Phase 1]					
SAGE-421		NMDA Hypofunction	[Progress bar: Preclinical]					



Light shades indicate trials in the planning or evaluation stage

Depression



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 them¹

1

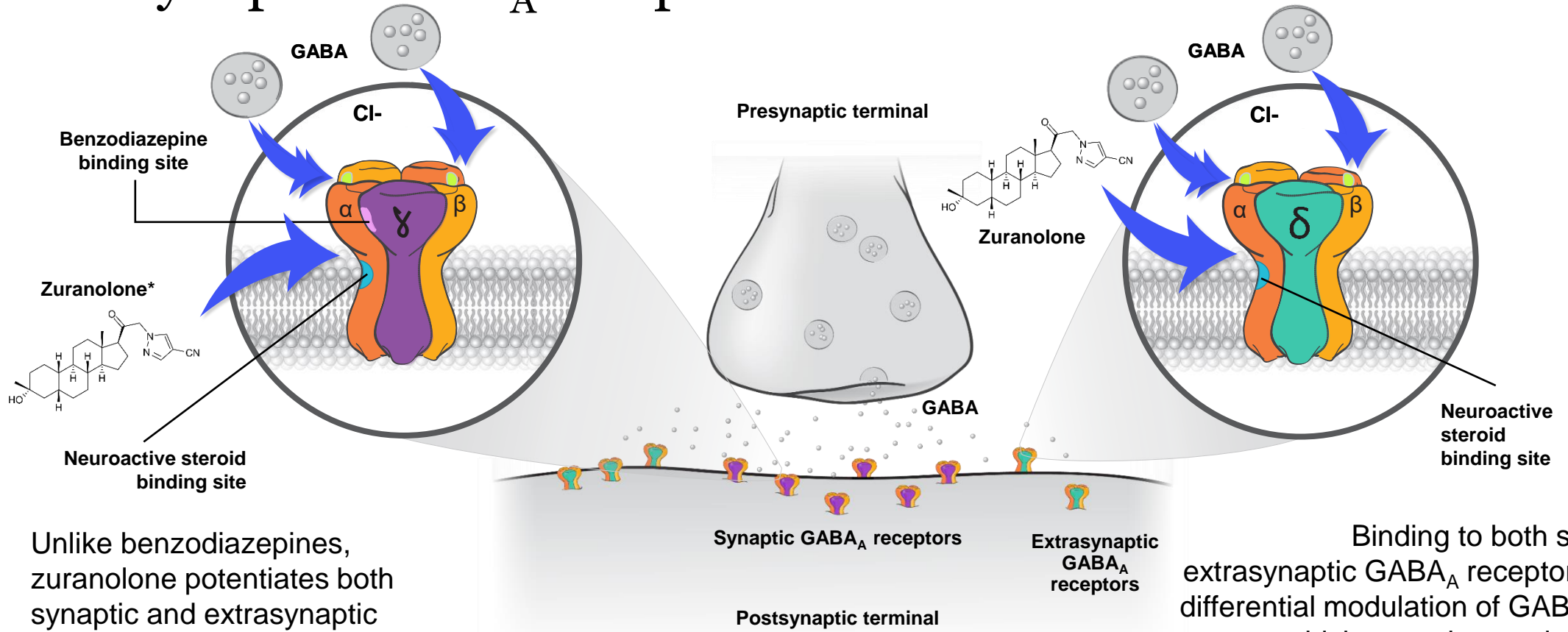
STAR*D Analysis shows that patients who achieve later remission have a 1.5 times higher risk of relapse than those who remit early¹

2

The economic burden of MDD in the United States is an estimated \$326 billion in 2018²

3

Zuranolone is a neuroactive steroid that binds to synaptic and extrasynaptic GABA_A receptors^{1,2}



Unlike benzodiazepines, zuranolone potentiates both synaptic and extrasynaptic GABA_A receptor activity in vitro³

Binding to both synaptic and extrasynaptic GABA_A receptors allows for differential modulation of GABA signaling, which may play a role in restoring adaptive signaling in the brain³

Figure adapted from Jacob et al.¹ and Reddy et al.²

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

Rapid & Sustained

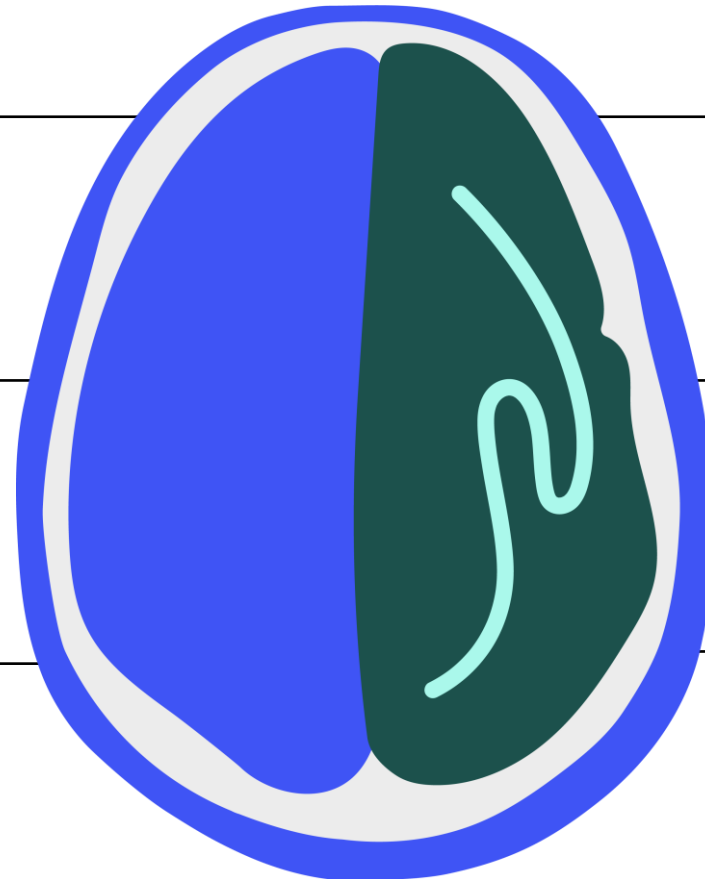
- Rapid symptom reduction observed
- Sustained effects lasted beyond completion of treatment

Well-Tolerated

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

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 rebalance¹

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.

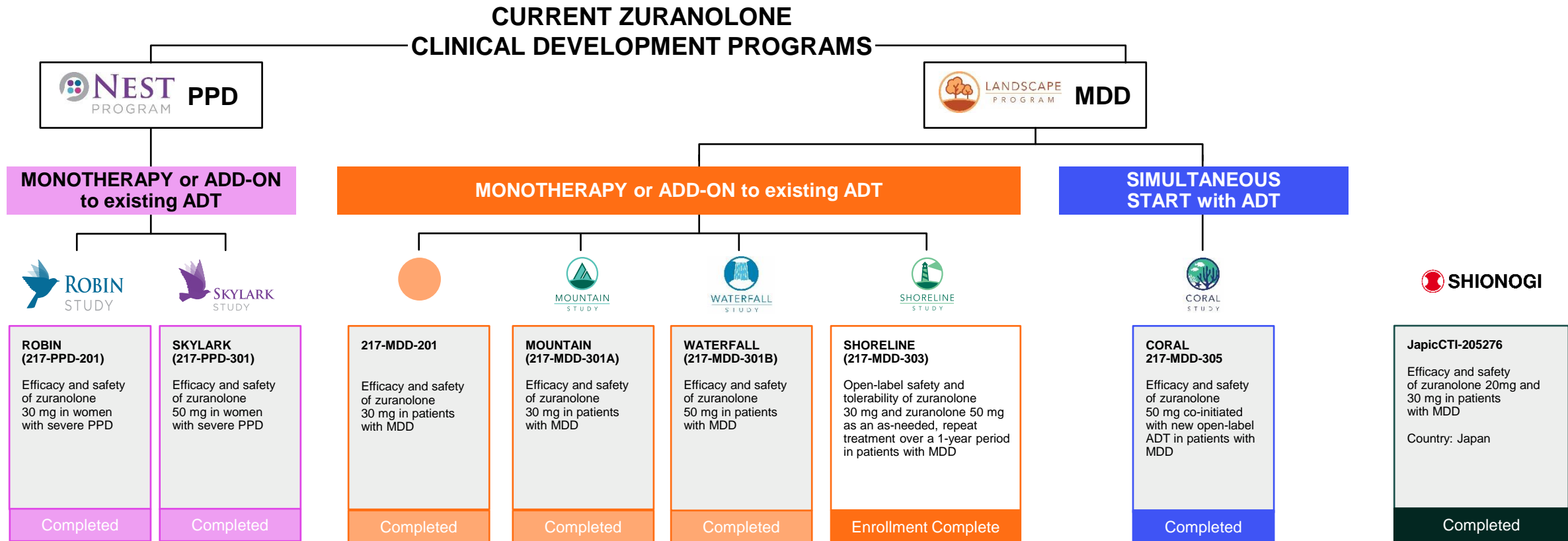
¹Antonoudiou, P. et al. Allopregnanolone mediates affective switching through modulation of oscillatory states in the basolateral amygdala. *Biological Psychiatry*, 2021.2003.2008.434156, doi:10.1016/j.biopsych.2021.07.017 (2021).

MDD = major depressive disorder, PPD = postpartum depression

Zuranolone is being developed in collaboration with Biogen.

Zuranolone Clinical Development Programs

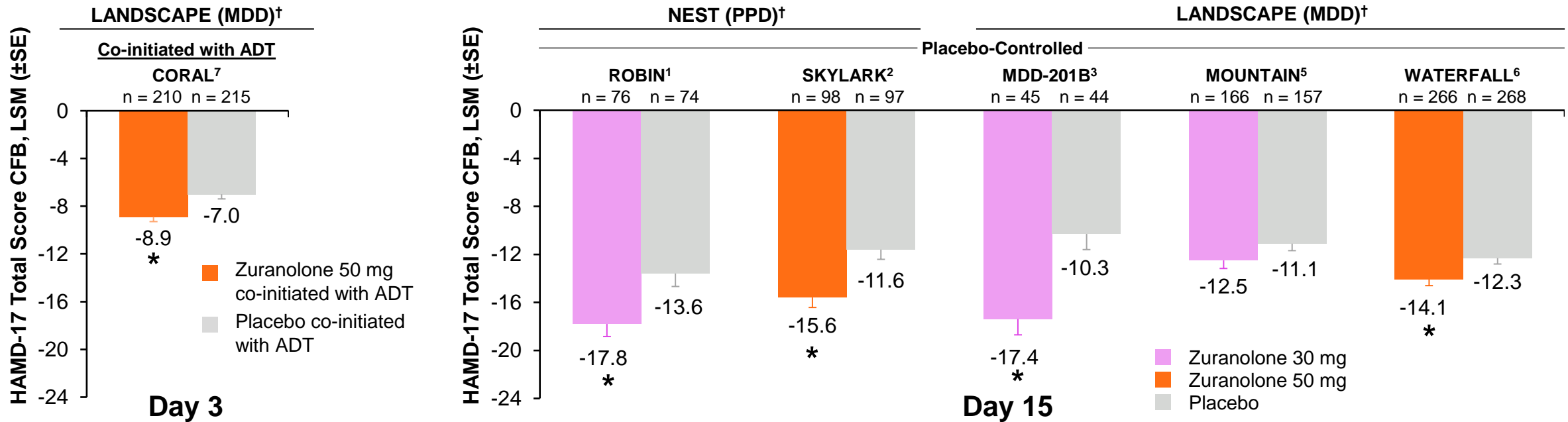
Potential to reshape the depression landscape



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

Primary Endpoints in Zuranolone Placebo-Controlled Trials

The Primary Endpoint for CORAL was CFB in HAMD-17 at Day 3, and the Primary Endpoint for ROBIN, SKYLARK, MDD-201B, MOUNTAIN, and WATERFALL was CFB in HAMD-17 at Day 15.¹⁻⁷



- The clinical trials above differ in sample size, patient population, entry criteria, and study sites as well as other design elements. No direct comparison can be made across these clinical trials based on the graph above. ROBIN and SKYLARK enrolled patients with PPD; MDD-201B, MOUNTAIN, WATERFALL, and CORAL enrolled patients with MDD.^{1-4,6,7}

*p<0.05 vs placebo; p values for the LSM treatment difference were statistically significant for all studies shown except in the MOUNTAIN Study. †n = number of patients included in the FAS.

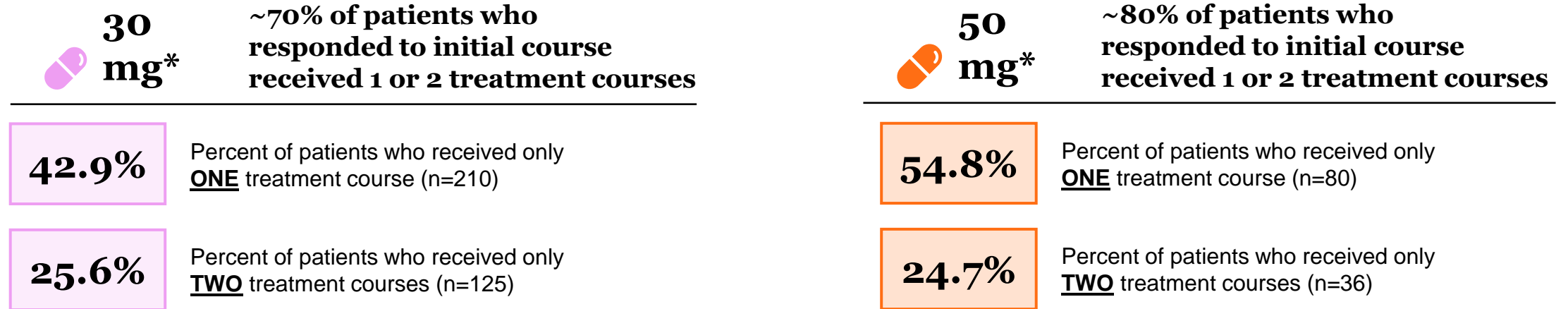
ADT = antidepressant therapy; CFB = change from baseline; FAS = Full Analysis Set; HAMD-17 = 17-item Hamilton Rating Scale for Depression total score; LSM = least squares mean; MDD = major depressive disorder; PPD = postpartum depression; SE = standard error.

1. Deligiannidis KM, et al. *JAMA Psychiatry*. 2021;78(9):951-959. 2. Deligiannidis et al. Efficacy and safety of zuranolone 50 mg in postpartum depression: SKYLARK Study, a double-blind, placebo-controlled randomized, phase 3 study. Oral presentation presented at ECNP Vienna, Austria Oct 16 2022. 3. Gunduz-Bruce H, et al. *N Engl J Med*. 2019;381(10):903-911. 4. Mittal A, et al. Poster presented at: American Academy of Neurology Annual Meeting; 25 Apr-01 May 2020; Toronto, Canada. 5. Data on file. MOUNTAIN Study (217-MDD-301) CSR. 16 Apr 2021.

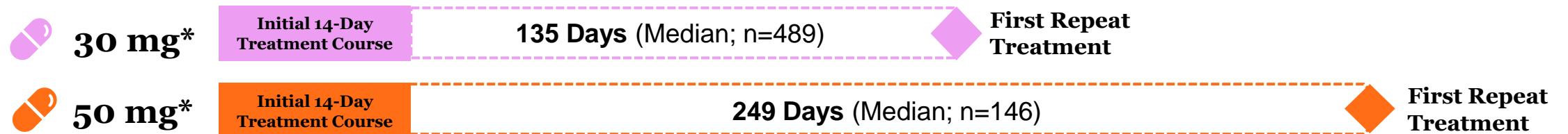
6. Clayton AH, et al. Poster presented at: Psych Congress Annual Meeting; 29 Oct-01 Nov 2021; San Antonio, TX. 7. Parikh SV, et al. Poster presented at: American Society of Clinical Psychopharmacology Annual Meeting; 31 May-03 Jun 2022; Scottsdale, AZ.

Zuranolone Showed Potential for Sustained Effects in the SHORELINE Study

Patients had the opportunity to be followed for up to 12 months



Median Time to First Repeat Treatment



- Number of additional treatment courses was similar in patients using zuranolone as monotherapy or add-on therapy (without or with pre-existing antidepressants).¹
- The SHORELINE Study was designed to evaluate efficacy in an observational manner, and therefore, statistical inferences cannot be drawn from efficacy outcome data.³

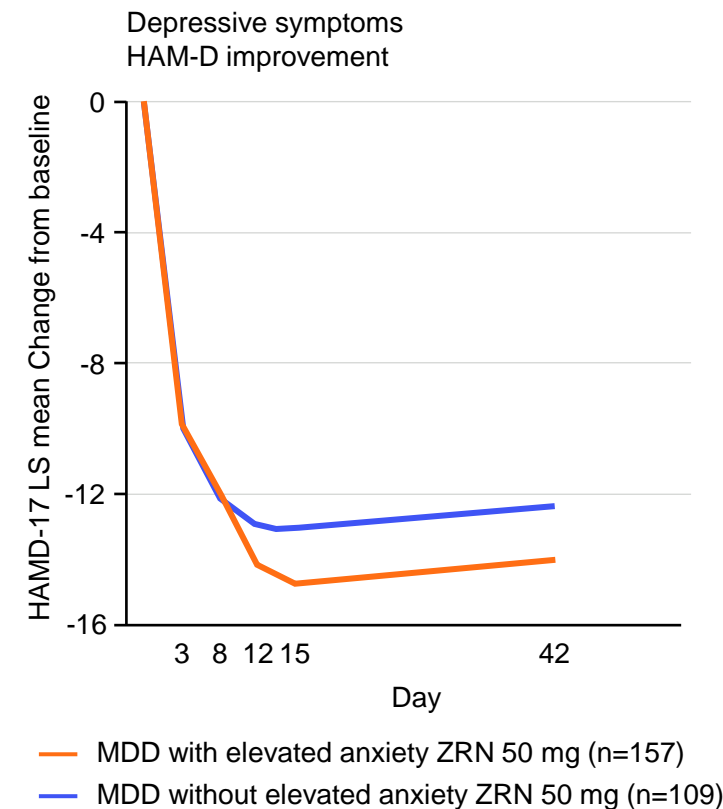
Note about Study Design: Only responders (≥50% reduction in HAMD-17 total score from baseline) at Day 15 of the initial treatment period can continue in the SHORELINE Study.

Need for repeat treatment courses is first assessed by PHQ-9 every 2- weeks. If PHQ-9 ≥10, a HAMD-17 assessment is performed within 1 week. If HAMD-17 total score ≥20, a repeat treatment course may be initiated. There is a minimum of 8 weeks between treatment periods, to allow for a maximum of 5 treatment courses for the 1-year study period; a new repeat treatment course cannot start after Week 48.¹ *30 mg Cohort includes a 30 mg Only Group (patients who received repeat treatment courses with zuranolone 30 mg) and a 30 mg Dose Switch Group (patients who received repeat treatment courses with zuranolone 50 mg). ¹De novo patients who enrolled into the 50 mg Cohort by September 2020 and had the opportunity to complete 1-year follow-up. The full analysis set consisted of 146 patients who were responders at Day 15 and completed the initial treatment cycle.¹
 1. Data on file. SHORELINE Topline results memo (November 2021). 2. Clayton et al. Sustained Benefits of Zuranolone in Patients With Major Depressive Disorder: Results From the LANDSCAPE Clinical Development Program poster presented Sept 18 at Psych Congress 2022 New Orleans, LA. 3. Cutler AJ et al. Presented at Society of Biological Psychiatry Annual Meeting, 2021 Virtual Meeting; April 29-May 1, 2021.

Zuranolone has the potential to address MDD patient populations, like those with MDD with elevated anxiety, for whom standard of care doesn't fully address unmet need

- Continued unmet need evidenced by majority of LANDSCAPE program participants meeting criteria for MDD with elevated anxiety
 - Assessed at baseline by elevated anxiety and somatization symptoms in the setting of MDD (e.g., HAM-D-17, HAM-A scales)
 - Improvements in depression and anxiety symptoms observed when elevated anxiety is – or is not – present
- Well-established that MDD with elevated anxiety as a symptom is associated with:
 - More severe illness
 - More difficulty tolerating antidepressants, potentially impacting adherence
 - Higher rates of non-response to treatment, and greater need for additional interventions and resources

WATERFALL Study: Zuranolone Significantly Improved Depression Symptoms



Short Form-36 Patient Reported Outcome Health Survey

What is SF-36?¹

- SF-36 is a validated patient reported outcome instrument that allows for insights into how patients perceive their profile of functional health and well-being²
- Widely recognized as being among the leading patient-reported outcomes measures
 - Allows assessment of how a person perceives the impact of a disease on their well-being and functioning, and how that evolves with treatment
- The SF-36 has been used as an efficacy endpoint in clinical trials as well as an instrument to assess health states for health economics evaluations of new products and is well documented in the published scientific literature

What does SF-36 generate?

- SF-36 generates 8 domains and health economics utilities:
 - Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional, Mental Health

Physical Health

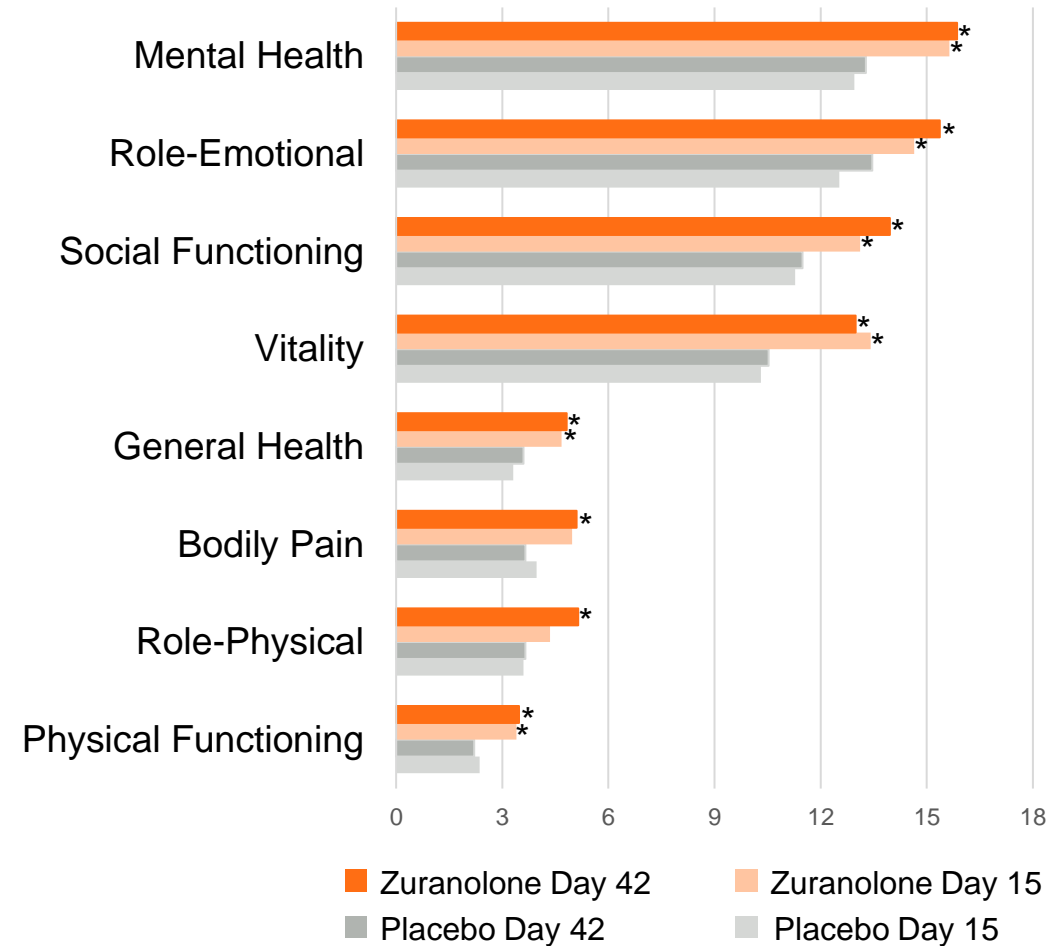
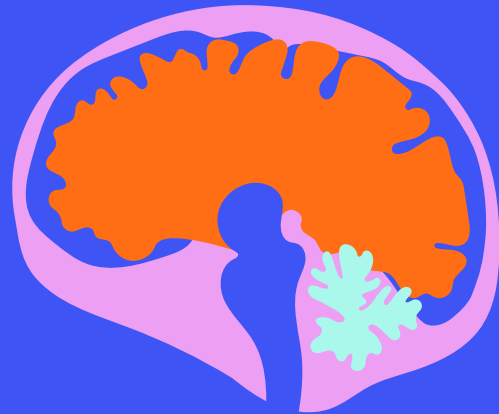
Physical Function	Role Physical	Bodily Pain	General Health
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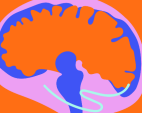
Mental Health

Vitality	Social Functioning	Role Emotional	Mental Health
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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





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

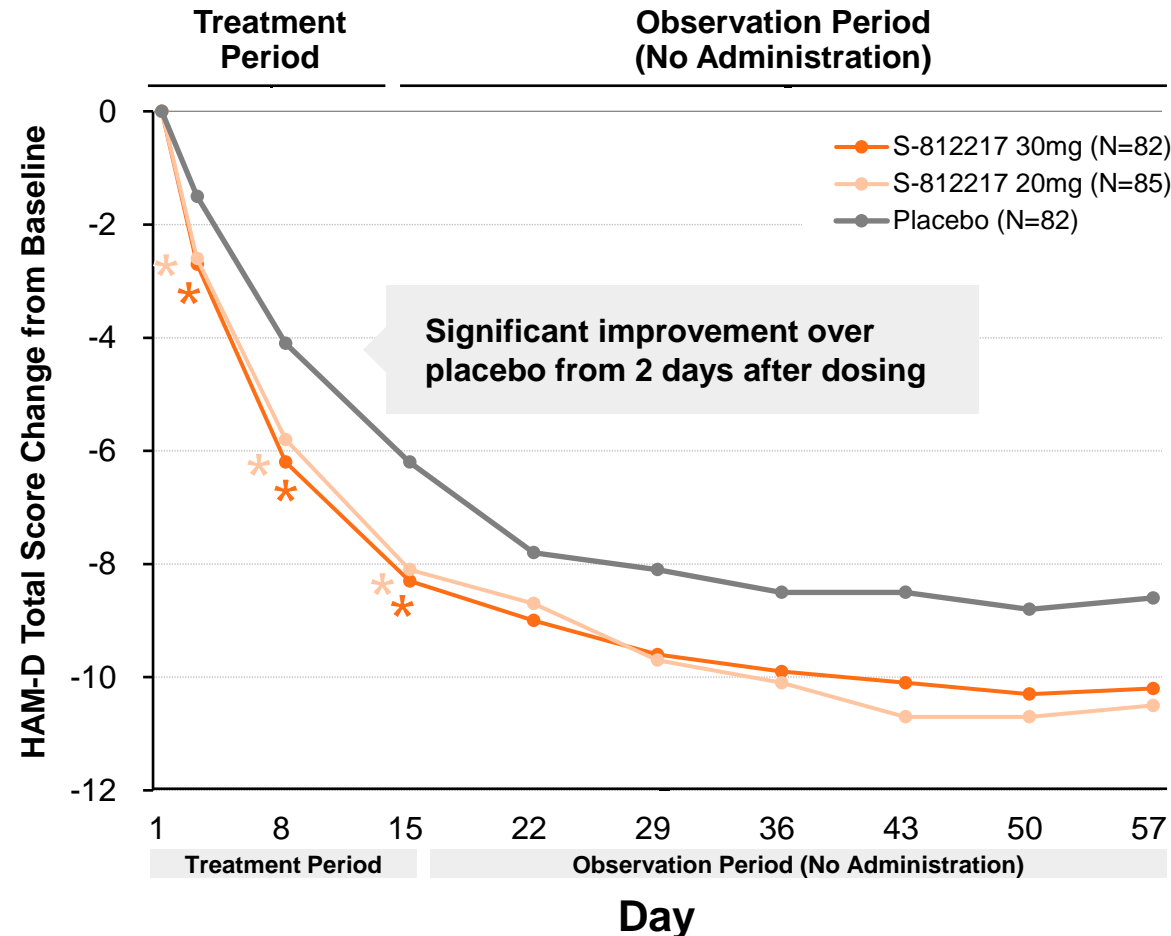
Among patients treated in the ongoing open-label Phase 3 SHORELINE Study, the most common TEAEs (>5%) observed in the 30 and 50 mg cohorts were headache, somnolence, dizziness, and sedation. Patient experiences are provided solely to help illustrate the data collected from the SHORELINE Study interviews. 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.

Shionogi Phase 2 Study conducted in Japan shows consistent profile of zuranolone



Efficacy

- **Achieved the primary endpoint at both 20 mg and 30 mg**
 - Significant improvement over placebo from Day 3 (first observation) to Day 15 (end of administration) at 20 mg and 30 mg of change in total HAM-D score from baseline
 - Response rate** was significantly improved on Day 8 and Day 15 compared to placebo
 - ⇒ **Confirmed the "Quick onset"**
 - Throughout the observation period from Day 15 to Day 57, although there was no significant difference from placebo, trend in continuous therapeutic effect was observed.

Safety

- **Confirmed the safety**
 - All adverse events were mild or moderate, with no new concerns

A 14-Day Treatment Course with Zuranolone 30 mg or 50 mg was Generally Well-tolerated in Patients with MDD or PPD¹⁻⁵

- Safety and tolerability of zuranolone in patients with MDD or PPD were generally consistent across studies during the 14-day treatment course.¹⁻⁵
 - The most common AEs (>10%) reported with zuranolone included headache, somnolence, dizziness, nausea, and sedation.¹⁻⁵
 - SAEs occurred in <5% of zuranolone-treated patients across all clinical trials of zuranolone.^{1,2,6,7}
 - To date (10/2022), there have been no signals of suicidal ideation or symptoms of withdrawal. In addition, weight gain and sexual dysfunction were not identified as safety concerns associated with zuranolone.¹⁻⁵
- Treatment discontinuation rates due to AEs resulting from treatment with zuranolone were <5% in ROBIN, SKYLARK, MDD-201B, MOUNTAIN, and WATERFALL and <10% in SHORELINE and CORAL Studies.^{1,2,5-8}

Range of TEAEs Across All Phase 2 and 3 Trials^{1-5,*} ROBIN, SKYLARK, MDD-201B, MOUNTAIN, WATERFALL, SHORELINE,[†] and CORAL Studies

Severity of TEAEs, % (overall range)	Zuranolone 30 mg or 50 mg [‡] (N = 1737)
Mild to moderate	85-100
Severe	0-10
Serious	0-5
Most Common (>10%) TEAEs, % (overall range)	
Headache	6-18
Somnolence	7-27
Dizziness	5-15
Nausea	3-11
Sedation	4-11

Note: Represents composite safety information across clinical trials in different patient populations and different doses.

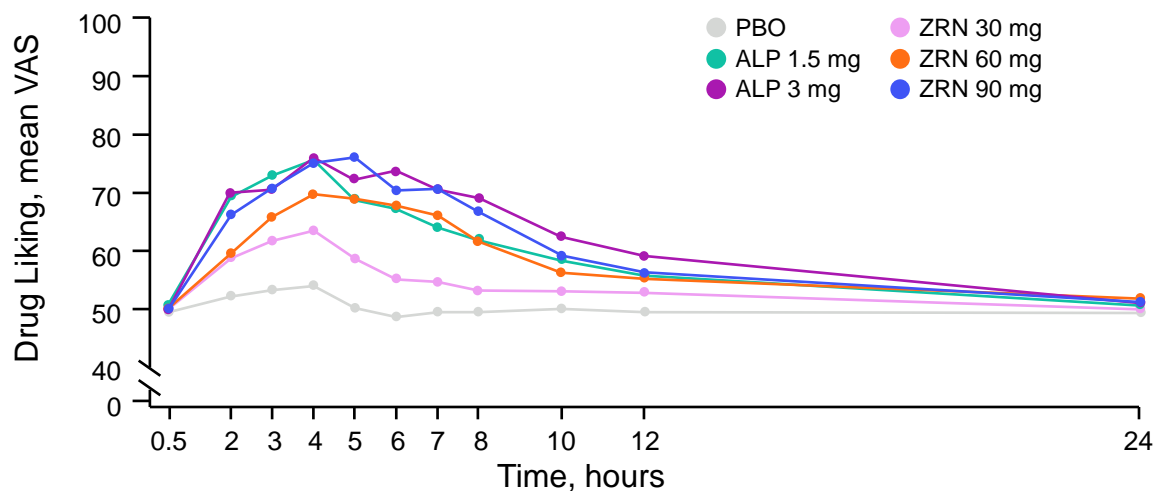
*The most common TEAEs were defined as having occurred in >10% of patients receiving either zuranolone 30 mg or 50 mg; TEAEs for the SHORELINE Study were included for the 30 mg Only Group and 50 mg Cohort as of the 11 Nov 2021 data cut;^{4,5} in the CORAL Study, zuranolone 50 mg was co-initiated with an ADT (which could be continued after the 14-day treatment course).³ †Overall population (N = 924); complete data for the 30 mg Cohort (n = 725; 30 mg only [n = 645] and 30 mg/50 mg dose-switch [n = 80] groups); interim data for the 50 mg Cohort (n = 199) who had the opportunity to complete 1 year follow-up as of the 11 Nov 2021 data cut.^{4,5} ‡ROBIN: n = 78 (ZRN 30 mg);¹ SKYLARK: n = 98 (ZRN 50 mg);² MDD-201B: n = 45 (ZRN 30 mg);¹ MOUNTAIN: n = 192 (ZRN 30 mg);¹ WATERFALL: n = 268 (ZRN 50 mg);¹ SHORELINE: n = 645 (ZRN 30 mg ONLY) and n = 199 (ZRN 50 mg);^{4,5} CORAL: n = 212 (ZRN 50 mg co-initiated with an ADT).³

ADT = antidepressant therapy; AE = adverse event; MDD = major depressive disorder; PPD = postpartum depression; TEAE = treatment-emergent adverse event; SAE = serious adverse event; ZRN = zuranolone.

1. Deligiannidis KM, et al. Poster presented at: American Society of Clinical Psychopharmacology Annual Meeting; 31 May-03 Jun 2022; Scottsdale, AZ. 2. Data on file. SAGE-217-PPD-301 Topline Statistical Results Memo, Version 1.0. 25 May 2022. 3. Parikh SV, et al. Poster presented at: American Society of Clinical Psychopharmacology Annual Meeting; 31 May-03 Jun 2022; Scottsdale, AZ. 4. Cutler AJ, et al. Poster presented at: Society of Biological Psychiatry Annual Meeting; 29 Apr-01 May 2021; Virtual congress. 5. Cutler AJ, et al. Poster presented at: Society of Biological Psychiatry Annual Meeting 28-30 Apr 2022; New Orleans, LA. 6. Data on file. CORAL Study Topline Statistical Results Memo; Protocol: SAGE-217-MDD-305, Version 3.0. 23 Feb 2022. 7. Data on file. Topline Statistical Results Memo: SAGE-217-MDD-303. 23 Nov 2021. 8. Clayton A, et al. Oral presentation at: European College of Neuropsychopharmacology Annual Meeting (New Medications Symposium); 02-05 Oct 2021; Lisbon, Portugal.

Zuranolone Exhibited Less Abuse Potential than Alprazolam at 30 mg and 60 mg Doses*

Mean VAS scores for Drug Liking Over Time⁷



Study design & disposition

- Dose selection phase: Dose escalation in 3 cohorts (60 mg + PBO, 80 mg + PBO, 90 mg + PBO); N=23 completed the dose selection phase⁷
- Treatment phase: Randomized, double-blind active and PBO-controlled, 6-way crossover design; N=60 completed treatment phase⁷

- Zuranolone 30 mg and 60 mg demonstrated lower abuse potential compared with alprazolam 1.5 mg and 3mg⁷
- Zuranolone 90mg was comparable to alprazolam⁷

- Mean Drug Liking VAS scores for zuranolone 30 mg, 60 mg, and 90 mg increased over time, with peak effects observed 4-5 hours post dose, and zuranolone 30 mg scores remaining below those of alprazolam⁷
- Zuranolone 30 mg and 60 mg demonstrated significantly lower Drug Liking E_{max} vs alprazolam 1.5 mg and 3 mg (p <0.05 for all comparisons)⁷
- Human abuse potential (HAP) studies are part of evaluation of abuse potential for all CNS-active drugs required by the U.S. Food and Drug Administration.⁶

*In non-dependent, recreational users of CNS depressants: A double-blind, active- and placebo-controlled cross over Phase 1 study

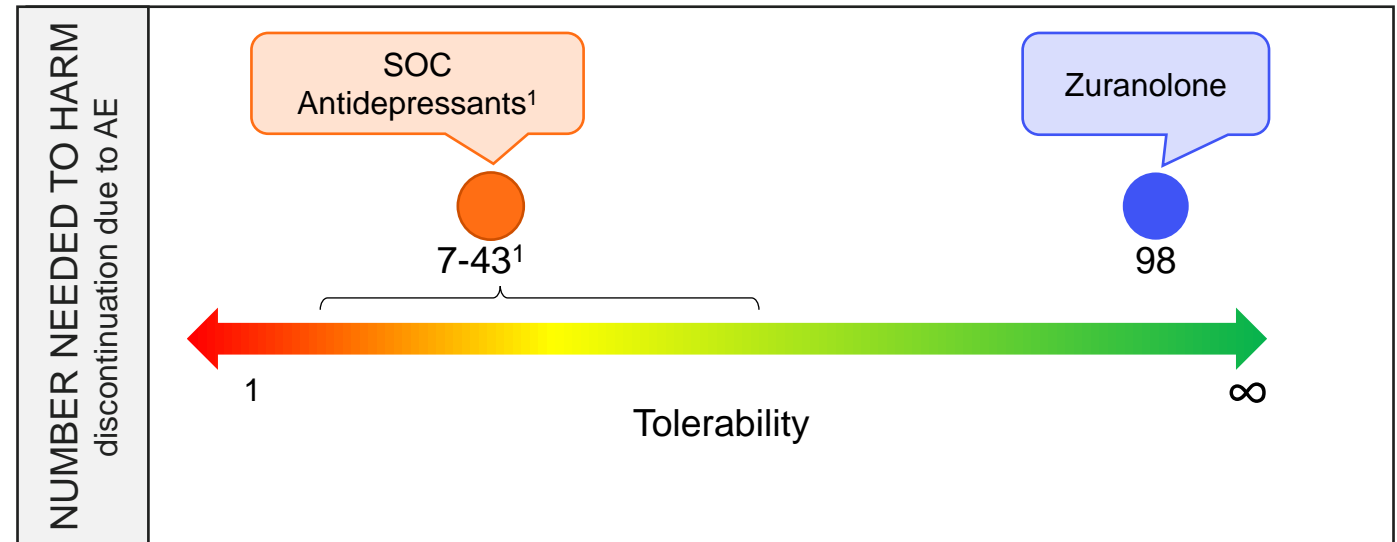
ALP, alprazolam; CNS, central nervous system; GABA_AR, γ-aminobutyric acid receptors; PBO, placebo; US FDA, United States Food and Drug Administration; VAS, visual analog scale, ZRN, zuranolone
 1. Alhaus AL, et al. Neuropharmacology; 2020. 2. Martinez Botella G, et al. Med Chem. 2017. 3. Schwientek KL, et al. Psychopharmacology. 2017. 4. Hoffmann E, et al. Clin Pharmacokinet. 2020. 5. Nicholson MW, et al. Mol Psychiatry. 2018. 6. Center for Drug Evaluation and Research (n.d.) Assessment of abuse potential of drugs. US FDA. Retrieved 9 May 2022. 7. Dunbar et al. CPDD 2022.
 Zuranolone is being developed in collaboration with Biogen.

NNH Analysis of Placebo-controlled LANDSCAPE* and NEST Programs

Number needed to harm: Numerical estimate of treated patients for one additional discontinuation due to an adverse event

Discontinuation due to AEs is commonly utilized in MDD for NNH calculations

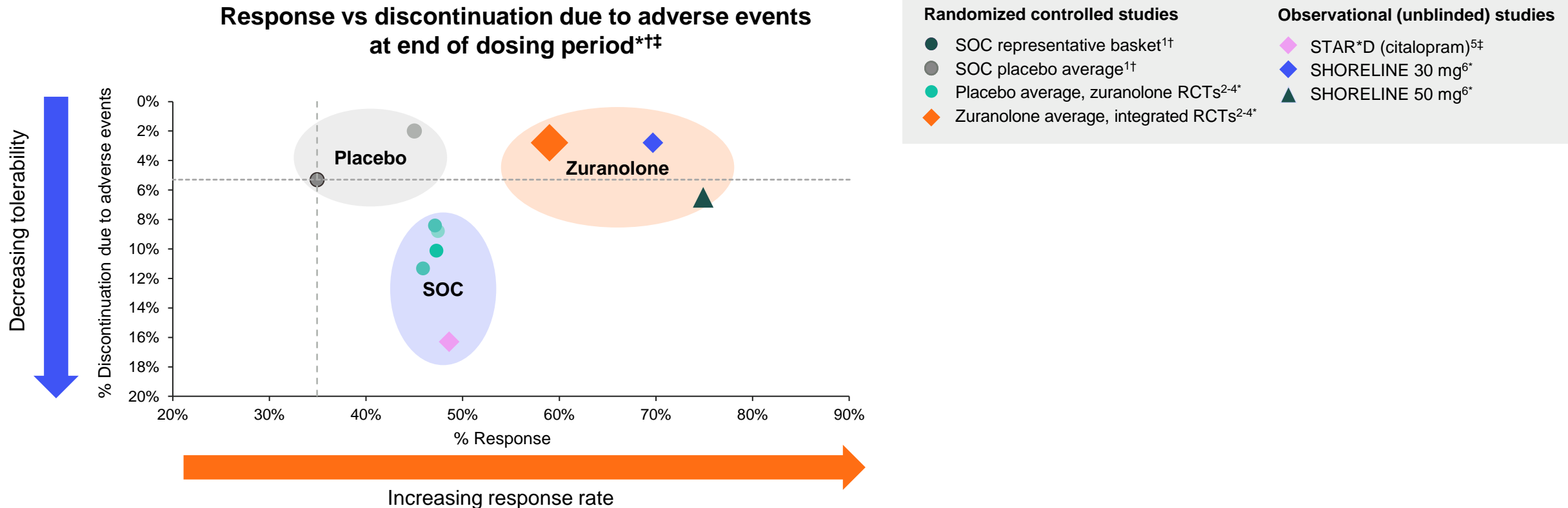
Discontinuation due to adverse event rates		
	Placebo	Zuranolone (30mg and 50mg)
MDD-201B	0.0%	4.4%
ROBIN Study	0.0%	1.3%
MOUNTAIN Study	3.2%	2.1%
WATERFALL Study	1.5%	3.4%
Weighted average (by n)	1.7%	2.8%



Number Needed to Harm (NNH) = $1 / (\%Discontinuation_{217} - \%Discontinuation_{PBO})$
 $NNH = 1 / (0.02765799 - 0.0174489) = 98$

Discontinuation rates due to adverse events reported here are indirect comparisons derived from different studies.

Potential benefit-risk profile of zuranolone may be distinct from current antidepressants



The clinical trials above differ in sample size, patient population, entry criteria, study sites as well as other design elements. No direct comparison can be made across these clinical trials based on the graph to the left

The MDD landscape presents significant opportunity for a new therapy to help patients who are not satisfied with current treatment

MDD Patient Opportunity

Adults with a Major Depressive Episode

~21 M¹

▼ 66%

Diagnosed & Treated MDD Patients

~14 M¹

▼ 75%

Rx-Treated MDD Patients

~10.5 M¹

▼ 62%

MDD Patients Making a Treatment Change

~6.5 M²

Planned launch focus on subset of these patients



Figure not to scale. All patient numbers are estimates based on data we have obtained from published literature which references market research, claims research or other sources in some cases applying our own assumptions and analyses. As is generally the case with prevalence/population calculations, there are other data, studies or analyses that reach different conclusions as to estimates or ranges. If the data and assumptions we use turn out to have been inaccurate, the actual number of patients in each segment may differ from our estimates.

1. SAMHSA: 2020 NSDUH Detailed Tables 2. Zhu L, et al. J Manag Care Spec Pharm. 2022 Nov.

There is a clear unmet need for patients experiencing PPD symptoms

Despite being a common mental health disorder,
Postpartum Depression (PPD) *may often go undiagnosed or untreated*

In the US, about **1 in 8** mothers experiences symptoms of PPD ¹

This equates to **~477K** women with a live birth experiencing PPD symptoms ²

~50% of PPD cases may go undiagnosed without appropriate screening ^{3,4}

▼
and less than **25%** of patients screened for PPD receive follow-up care ⁵⁻⁷



Planned launch approach designed to educate and engage stakeholders

Stakeholder Needs	Strategic Imperatives
Patients Rapid, durable therapy without stigmatizing side effects often associated with chronic treatments (e.g., sexual dysfunction/weight gain)	▶ Inspire people with MDD and PPD to talk to their HCP about zuranolone
HCPs Rapid, durable, well-tolerated therapy for a range of patients with MDD and PPD with limited access hurdles	▶ Mobilize targeted HCPs to identify and treat appropriate patient types in MDD and PPD early in the course of treatment
Payors Achieve budget predictability and cost containment for new MDD and PPD therapies	▶ Align with payers to increase budget predictability through innovative proactive Value Based Agreements with the goal of enabling those with MDD and PPD to access zuranolone quickly and affordably
Patient Advocacy and Policy Makers Education to advocate for and advance the standard of care for those who need more from MDD and PPD treatment	▶ Raise treatment expectations in MDD and PPD through grassroots efforts, leveraging policy interventions that have been proven effective in addressing access to treatment

Zuranolone has the potential to address a range of treatment needs in MDD and PPD, if approved

MDD CORE LAUNCH FOCUS

Current or Prior ADT Treatment[^]

Treatment Naïve

Treatment Resistant*

Zuranolone MDD: Start, Add or First Switch



MDD Patient With:

- Unresolved symptoms of depression
- Elevated anxiety
- Adherence or tolerability issues

Estimated Patient Burden:

- \$4.7k household income lost per year²
- 53% reduction in quality of life for patients with severe MDD³
- 2.7x more likely for children to develop MDD⁴

PPD CORE LAUNCH FOCUS

Current or Prior ADT Treatment

Treatment Naïve

Treatment Resistant*

Zuranolone PPD: First Line Therapy



PPD Patients Who Often Experience:

- Unresolved symptoms of depression
- Difficulty bonding with baby
- Anxiety
- Sleep disturbances

Estimated Patient Burden:

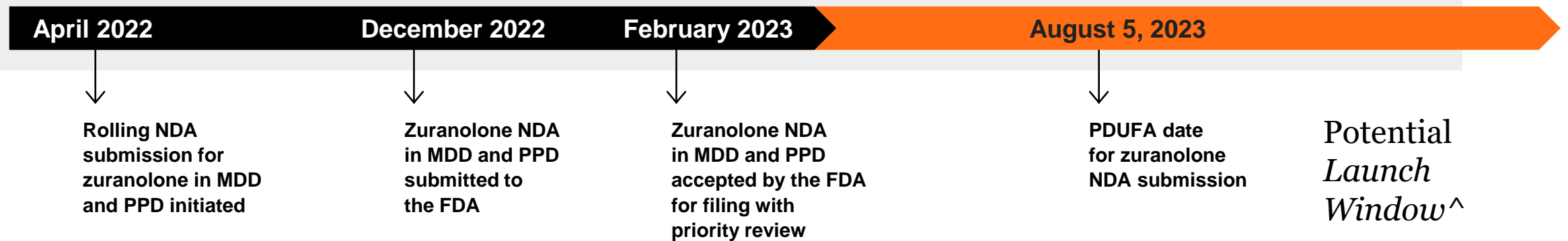
- Delayed or impaired long-term developmental, psychological, cognitive, and physical outcomes in children⁶⁻¹⁶
- \$31.8k average cost per child and mother affected⁵
- 24% to 50% of partners experience depression when a mother has PPD¹

[^]While physicians may prescribe across a wider MDD treatment range (e.g., treatment naïve, breakthrough episode, etc.), our launch focus will be on these specific MDD patient types. *Patients with treatment resistant depression were not included in zuranolone clinical trials and are outside the scope of planned marketing/promotional efforts.

1. Goodman JH. J Adv Nurs. 2004;45(1):26-35. 2. Population estimates were computed from the Vintage 2020 Monthly Postcensal Civilian Population census data. Source: United States Census Bureau. (2020). Monthly Postcensal Civilian Noninstitutionalized Population, July 2019 and July 2020. Retrieved January 18, 2022, from <https://www.census.gov/programs-surveys/popest/technical-documentation/research/evaluation-estimates/2020-evaluation-estimates/2010s-national-detail.html>. 3. Gao, K., Su, M., Sweet, J., & Calabrese, J. R. (2019). Correlation between depression/anxiety symptom severity and quality of life in patients with major depressive disorder or bipolar disorder. Journal of Affective Disorders, 244, 9–15. <https://doi.org/10.1016/j.jad.2018.09.063> 4. Aazh, Danesh, A. A., & Moore, B. C. J. (2019). Parental Mental Health in Childhood as a Risk Factor for Anxiety and Depression among People Seeking Help for Tinnitus and Hyperacusis. Journal of the American Academy of Audiology, 30(9), 772–780. <https://doi.org/10.3766/jaaa.18001>. 5. Luca DL, et al. Am J Public Health. 2020;110(6):888-896. 6. Eastwood JG et al. BMC Pregnancy Childbirth. 2012;12:148. 7. Yamaoka Y et al. Matern Child Health J. 2016;20(2):326-336. 8. Kerstis B et al. Arch Womens Ment Health. 2016;19(1):87-94. 9. Valla L et al. Infant Behav Dev. 2016;45(Pt A):83-90. 10. Koutra K et al. Soc Psychiatry Psychiatr Epidemiol. 2013;48(8):1335-1345. 11. Woolhouse H et al. Arch Womens Ment Health. 2016;19(1):141-151. 12. Netsi E et al. JAMA Psychiatry. 2018;75(3):247-253. 13. Hanington L et al. Child Care Health Dev. 2012;38(4):520-529. 14. Surkan PJ et al. BMC Pediatr 2014;14:185. 15. Verkuilij NE et al. Lancet Psychiatry. 2014;1(6):454-460. 16. Pearson RM et al. JAMA Psychiatry. 2013;70(12):1312-1319.

NDA for zuranolone accepted for filing, with multiple key milestones expected over the next 18 months

Planned activities and anticipated timelines



NDA development and related processes

DEA Scheduling Period (90 Days)[^]

Medical affairs, health economics, value and access, and commercialization planning

FDA indicated that it does not currently plan to hold an advisory committee for zuranolone

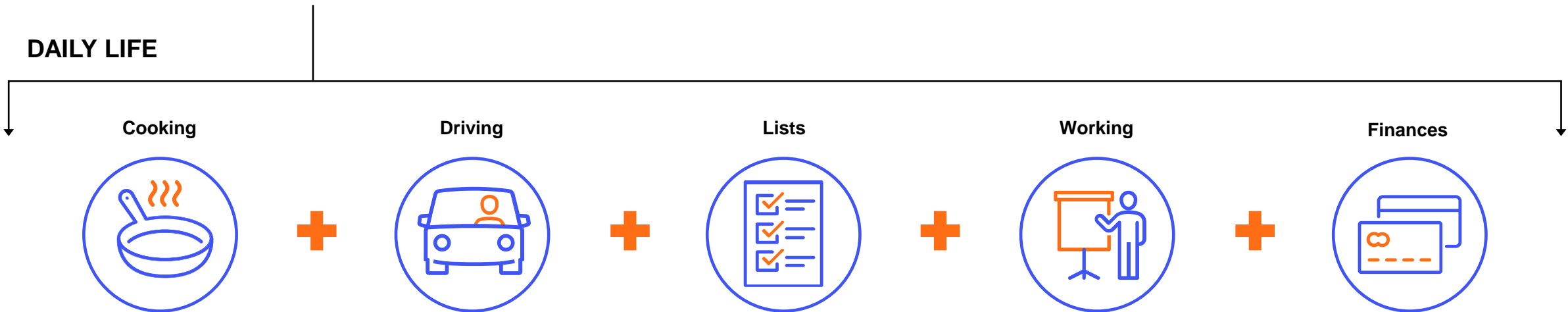
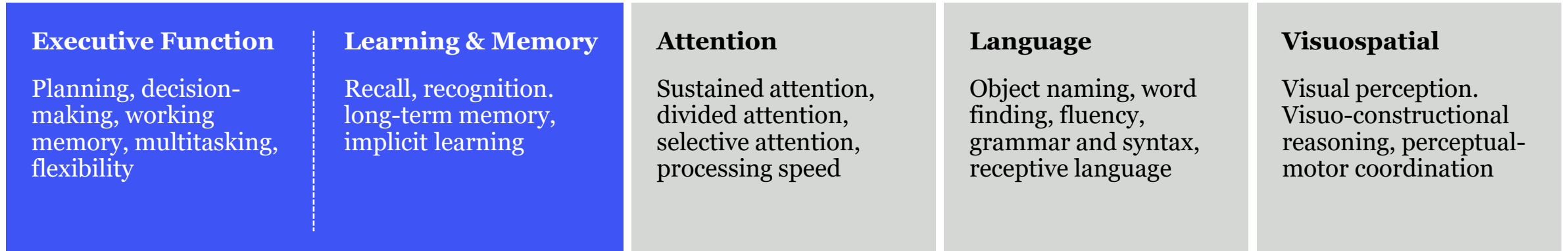
[^]Potential launch window and DEA scheduling period assumes approval and no review extensions

FDA = U.S. Food and Drug Administration; DEA = Drug Enforcement Administration; MDD = major depressive disorder; PPD = postpartum depression; NDA = new drug application

Neuropsychiatry

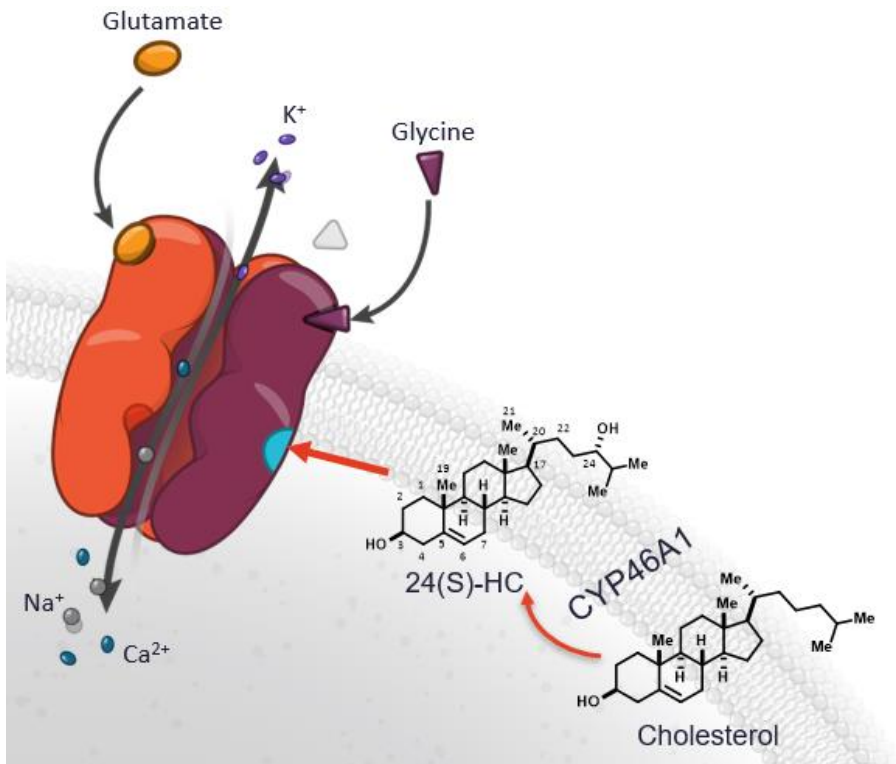


Cognitive impairment is prevalent and impacts people across the lifespan



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



Globally, disorders involving cognitive impairment continue to increase

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

~188K

Huntington's Disease Global Prevalence¹

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 Prevalence²

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

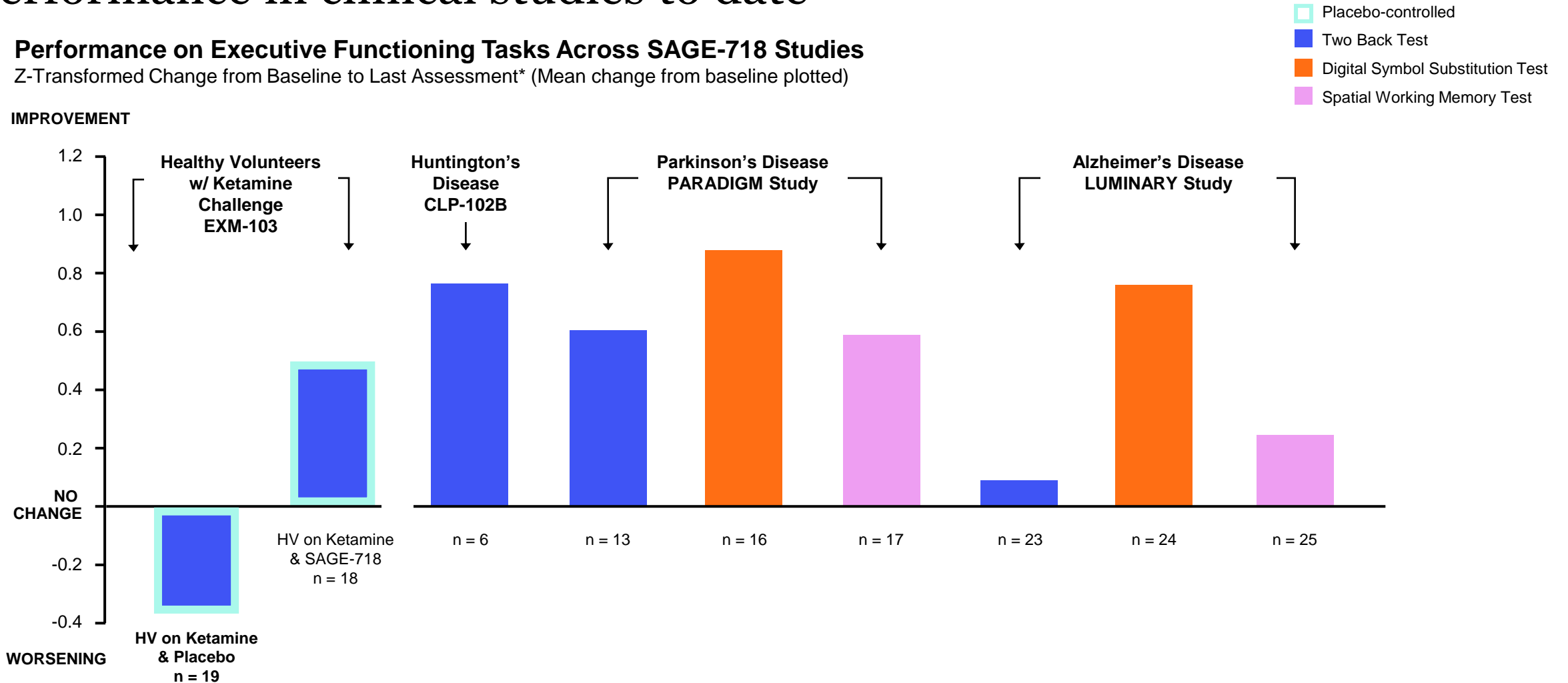
~134M

Alzheimer's Disease Global Prevalence³

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

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

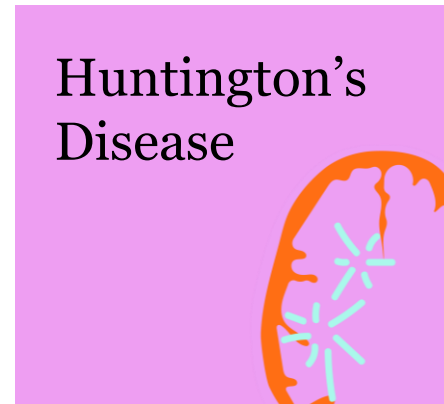
Performance on Executive Functioning Tasks Across SAGE-718 Studies
Z-Transformed Change from Baseline to Last Assessment* (Mean change from baseline plotted)



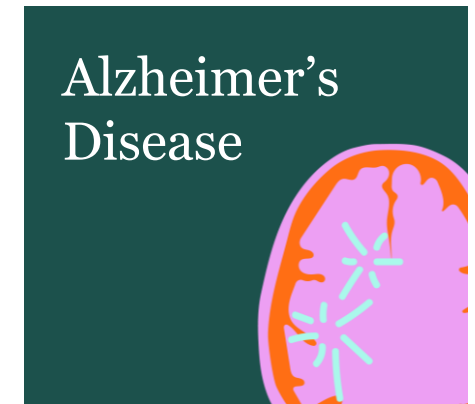
SAGE-718 clinical development program designed with goal to de-risk opportunities in multiple indications

- Huntington's disease is the initial indication for SAGE-718 development
- Fast Track Designation for SAGE-718 in Huntington's disease enables interactions to define an efficient potential path to registration in an orphan disease
- Advancing plans for further development including in Parkinson's and Alzheimer's diseases (studies ongoing in both indications)
- Leveraging learnings across indications designed to help de-risk program

Initial Indication

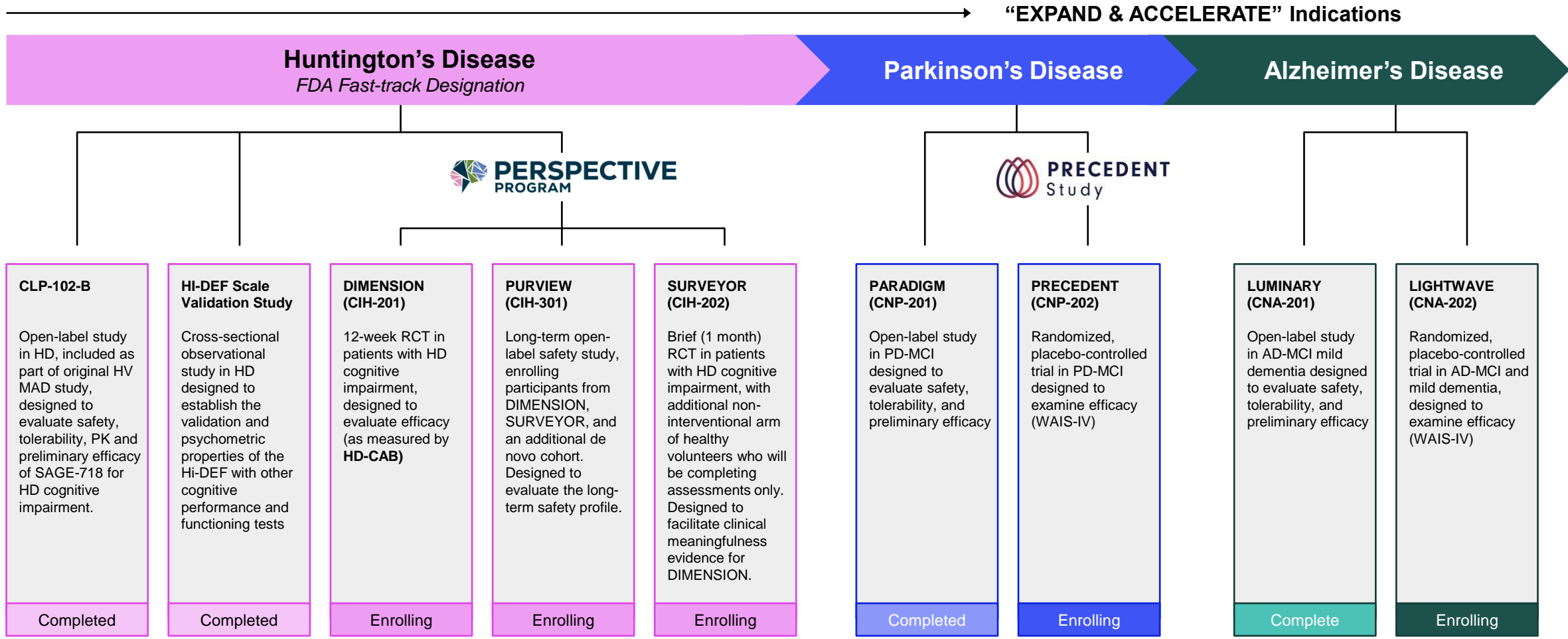


Additional Indications



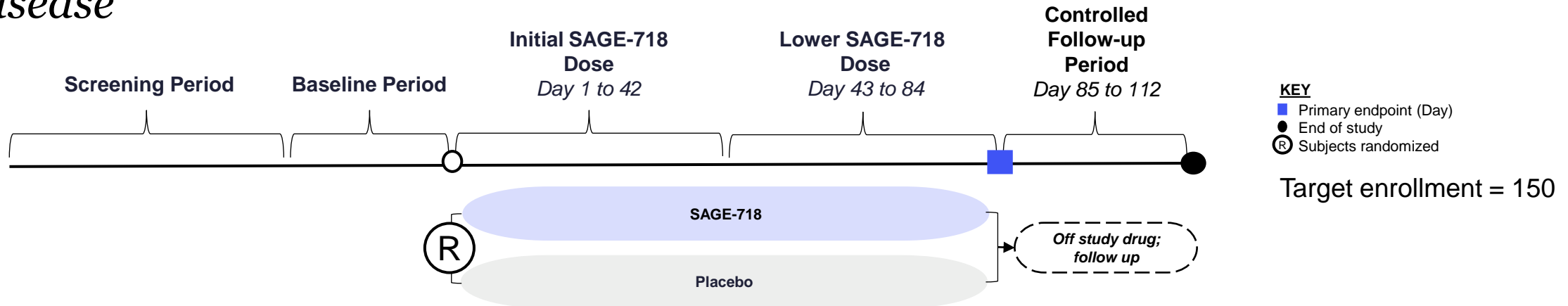
The SAGE-718 clinical development programs

Potential to reshape the treatment of patients with cognitive decline



LIGHTWAVE Study - SAGE-718

Placebo-controlled study in patients with MCI or Mild Dementia due to Alzheimer's Disease

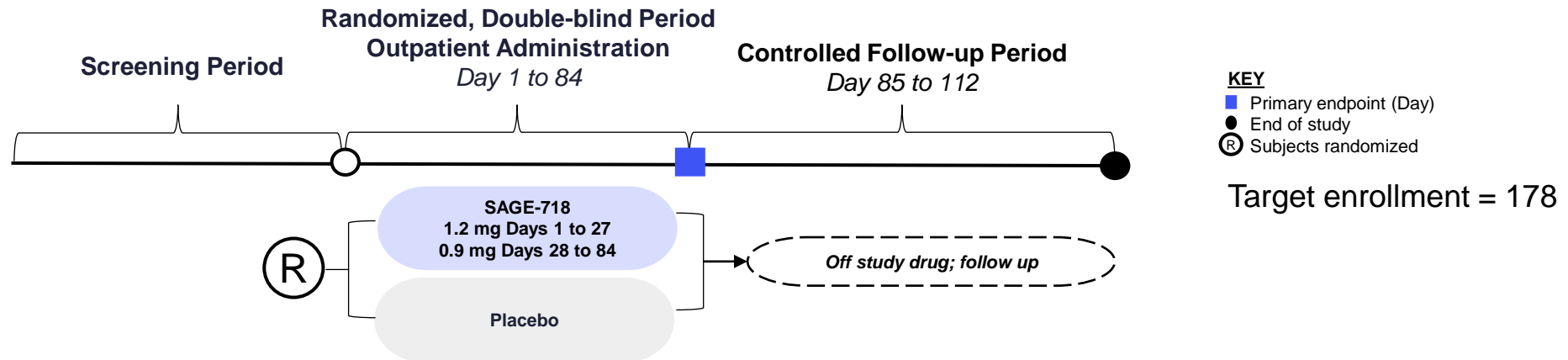


STUDY OVERVIEW

Status	Start-up	Objectives	<ul style="list-style-type: none"> To evaluate the effect of SAGE-718 on cognitive performance in participants with Mild Cognitive Impairment (MCI) or mild dementia due to Alzheimer's (AD) To evaluate the safety and tolerability of SAGE-718 oral capsule in participants with MCI or mild dementia due to AD
Indication	MCI or Mild Dementia due to Alzheimer's disease	Primary Endpoint	<ul style="list-style-type: none"> Change from Baseline to Day 84 in the Wechsler Adult Intelligence Scale-IV (WAIS-IV) Coding test
Phase	Phase 2	Key Secondary Endpoint	<ul style="list-style-type: none"> Additional endpoints to assess the effects of SAGE-718 on cognitive performance and functioning, including CGI-C, MoCA, CANTAB, and the Amsterdam Instrumental Activity of Daily Living questionnaire Proportion of participants experiencing treatment emergent adverse events (TEAEs) and severity of TEAEs Number of participants who withdraw due to adverse events (AEs)
Arms	Double-blind, randomized: 1:1 <ul style="list-style-type: none"> SAGE-718, placebo 	Inclusion Criteria	<ul style="list-style-type: none"> Be between the ages of 50 and 80 at Screening Meet all the following criteria for MCI or mild dementia due to AD: <ul style="list-style-type: none"> A memory complaint reported by the participant or their study partner A CDR score of 0.5 to 1.0 (inclusive) with a memory box score ≥ 0.5 Essentially preserved activities of daily living, in the opinion of the investigator Brain MRI report, obtained within the 2 years preceding the Baseline Period, which is consistent with the diagnosis of AD and with no clinically significant findings of non-AD pathology that could account for the observed cognitive impairment Have a MoCA score of 15 to 25 (inclusive) at Screening Have a study partner who, in the opinion of the investigator, is willing and able to provide informed consent, reliably support study-specific activities including IP adherence, be available by phone, and accompany the participant to study visits as needed If on concomitant medication, stable for at least 4 weeks prior to the first administration of study drug, and is expected to remain stable for duration of the study
Dosing Regimen	Initial Dose (Days 1 to 42), then Lower dose (Days 43 to 84)	Exclusion Criteria	<ul style="list-style-type: none"> Have participated in a previous clinical study of SAGE-718, have participated in a previous gene therapy study, or have received study treatment in any other drug, biologic, or device trial within 180 days or 5 half-lives (whichever is longer), unless the patient participated solely in the placebo arm of the study Have a medical or neurological condition (other than AD) that may be contributing to their cognitive impairment or history of cognitive decline

DIMENSION Study - SAGE-718

Placebo-controlled study in patients with early Huntington's disease

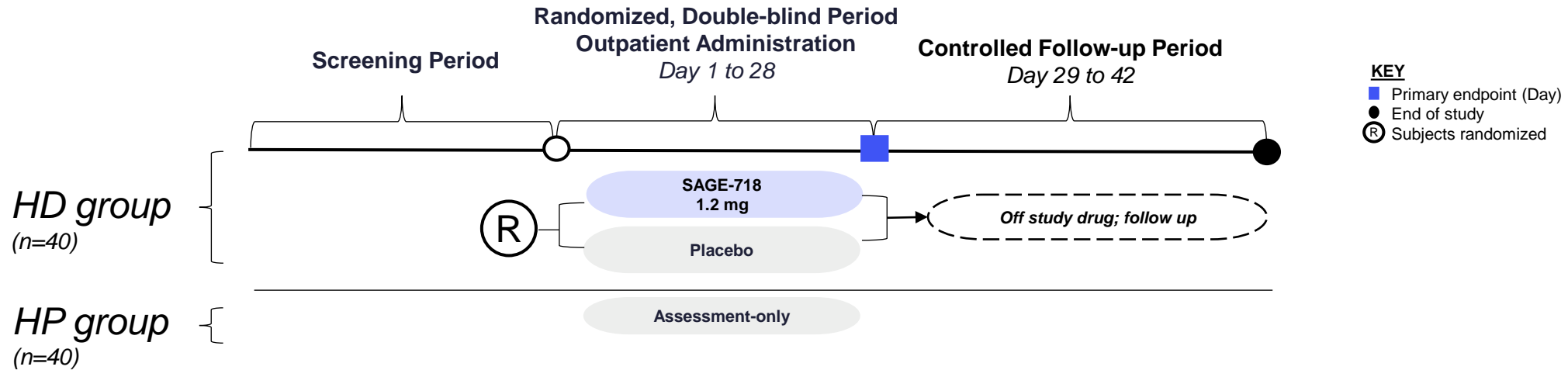


STUDY OVERVIEW

Status	Enrolling	Primary Endpoint	<ul style="list-style-type: none"> Change from baseline in Composite score of the Huntington's Disease Cognitive Assessment Battery (HD-CAB)
Indication	Huntington's disease Cognitive Impairment	Key Secondary Endpoint	<ul style="list-style-type: none"> UHDRS Independence Scale
Phase	Phase 2	Inclusion Criteria	<ul style="list-style-type: none"> Be at least 25 years old but no older than 65 years of age at Screening Meet all the following criteria for HD: <ul style="list-style-type: none"> Genetically confirmed disease with huntingtin gene CAG expansion ≥ 36 UHDRS-Total Functional Capacity (TFC) score >6 and <13 No features of juvenile HD Score <26 on the Montreal Cognitive Assessment (MoCA) at screening Be willing to invite a study partner, if available, who is reliable, competent, and at least 18 years of age to participate in the study Be ambulatory (use of assistance devices such as a walker or cane is acceptable; individuals requiring a wheelchair are excluded), able to travel to the study center, and, as judged by the investigator, is likely to be able to continue to travel to the study center to complete study visits for the duration of the study
Arms	Double-blind, randomized: 1:1 <ul style="list-style-type: none"> SAGE-718, placebo 	Exclusion Criteria	<ul style="list-style-type: none"> Have participated in a previous clinical study of SAGE-718, have participated in a previous gene therapy study, or have received study treatment in any other drug, biologic, or device trial within 180 days or 5 half-lives (whichever is longer), unless the patient participated solely in the placebo arm of the study Have a diagnosis of an ongoing neurodegenerative condition other than HD, including but not limited to, Alzheimer's disease, vascular dementia, dementia with Lewy bodies, or Parkinson's disease
Dosing Regimen	1.2 mg oral daily from days 1 to 27; 0.9 mg oral daily from days 28 to 84		

SURVEYOR Study - SAGE-718

PBO-controlled study in patients with early HD, with Healthy Participant (HP) Comparator Arm

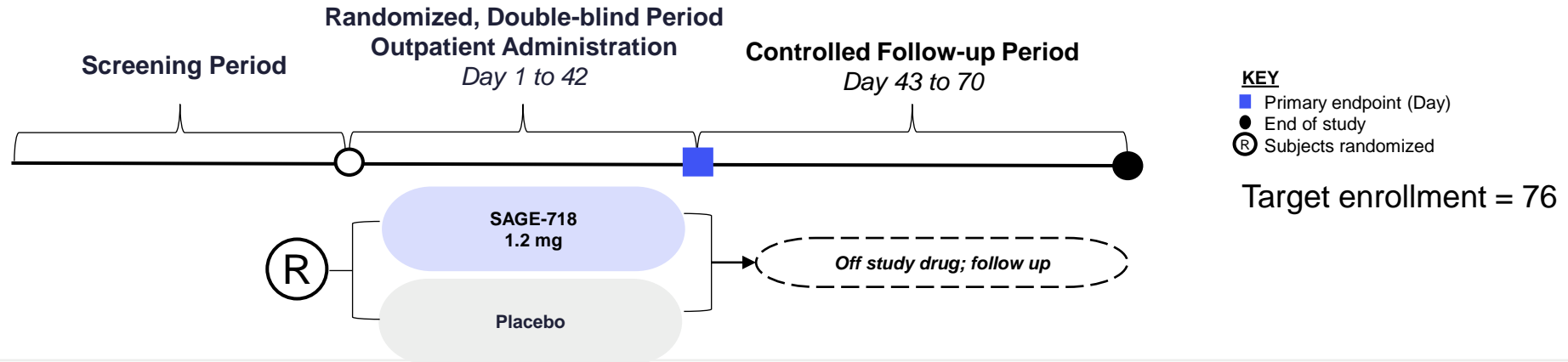


STUDY OVERVIEW

Status	Enrolling	Objectives	<ul style="list-style-type: none"> To assess the magnitude of the baseline difference between participants with early Huntington's Disease (HD) and healthy participants (HP) with respect to measures of cognitive performance. To evaluate the effect of SAGE-718 on cognition and functioning outcomes in participants with HD
Indication	Huntington's disease Cognitive Impairment	Primary Endpoint	<ul style="list-style-type: none"> Baseline measures of the Huntington's disease Cognitive Assessment Battery (HD-CAB) cognitive composite score.
Phase	Phase 2	Secondary Endpoints	<ul style="list-style-type: none"> Change from Baseline to Day 28 on HD-CAB, VRFCAT, other endpoints. Safety and tolerability of SAGE-718
Arms	Double-blind, randomized: 1:1 (HD) <ul style="list-style-type: none"> SAGE-718, placebo Assessment-only comparator arm (HP)	Inclusion Criteria (HD Participants)	<ul style="list-style-type: none"> Be at least 25 years old but no older than 65 years of age at Screening Meet all the following criteria for HD: <ul style="list-style-type: none"> Genetically confirmed disease with huntingtin gene CAG expansion ≥ 36 UHDRS-Total Functional Capacity (TFC) score >6 and <13 No features of juvenile HD Score <26 on the Montreal Cognitive Assessment (MoCA) at screening Be willing to invite a study partner, if available, who is reliable, competent, and able to participate in the study
Dosing Regimen	1.2 mg oral daily	Exclusion Criteria (HD Participants)	<ul style="list-style-type: none"> Have participated in a previous clinical study of SAGE-718, have participated in a previous gene therapy study, or have received study treatment in any other drug, biologic, or device trial within 90 days or 5 half-lives (whichever is longer), unless the patient participated solely in the placebo arm of the study Have a diagnosis of an ongoing neurodegenerative condition other than HD, including but not limited to, Alzheimer's disease, vascular dementia, dementia with Lewy bodies, or Parkinson's disease

PRECEDENT Study - SAGE-718

Placebo-controlled study in patients with MCI due to Parkinson's Disease



STUDY OVERVIEW

Status	Enrolling	Objectives	<ul style="list-style-type: none"> To evaluate the effect of SAGE-718 on cognitive performance in participants with Parkinson's Disease (PD) Mild Cognitive Impairment (MCI) To evaluate the safety and tolerability of SAGE-718 oral capsule in participants with PD-MCI
Indication	Mild Cognitive Impairment (MCI) due to Parkinson's disease	Primary Endpoint	<ul style="list-style-type: none"> Change from Baseline to Day 42 in the Wechsler Adult Intelligence Scale-IV (WAIS-IV) Coding test
Phase	Phase 2	Key Secondary Endpoint	<ul style="list-style-type: none"> Proportion of participants experiencing treatment emergent adverse events (TEAEs) and severity of TEAEs. Number of participants who withdraw due to adverse events (AEs).
Arms	Double-blind, randomized: 1:1 <ul style="list-style-type: none"> SAGE-718, placebo 	Inclusion Criteria	<ul style="list-style-type: none"> Be between the ages of 50 and 75 at Screening Meet all the following criteria for PD-MCI: <ul style="list-style-type: none"> Have a confirmed diagnosis of idiopathic PD according to 2015 MDS clinical diagnostic criteria, and Meet MDS Task Force Criteria for MCI in PD (excluding requirement for UK PD Brain Bank diagnostic criteria). For participants meeting Level 1 PD-MCI criteria, have a MoCA score of 20 to 25 (inclusive) at Screening For participants meeting Level 2 PD-MCI criteria, have a MoCA score of 18 to 25 (inclusive) at Screening Meet criteria for modified Hoehn and Yahr Stage I to III (mild to moderate motor severity) at Screening Have stable motor symptoms for at least 4 weeks prior to Screening, in the opinion of the investigator
Dosing Regimen	1.2 mg oral daily	Exclusion Criteria	<ul style="list-style-type: none"> Have participated in a previous clinical study of SAGE-718, have participated in a previous gene therapy study, or have received study treatment in any other drug, biologic, or device trial within 180 days or 5 half-lives (whichever is longer), unless the patient participated solely in the placebo arm of the study Have a diagnosis of dementia of any etiology, including but not limited to: Dementia associated with PD (probable or possible), Dementia with Lewy Bodies, Alzheimer's Dementia, and Vascular Dementia Have any parkinsonism other than PD, including secondary parkinsonism or atypical parkinsonism

Neurology



Movement and neurological disorders

Gaps remain in bringing effective treatments to people with movement disorders

- An estimated 136.4 million people globally suffer from essential tremor (ET) or Parkinson's disease (PD)
- Standards of care are inadequate for many people suffering from movement disorders
- Substantial mental health impact and caregiver burden

ET is strongly linked to impairment in Activities of Daily Living (ADL)

In patients with severe ADL impairment:

>90% of patients have difficulty with writing, eating, drinking, and self-care

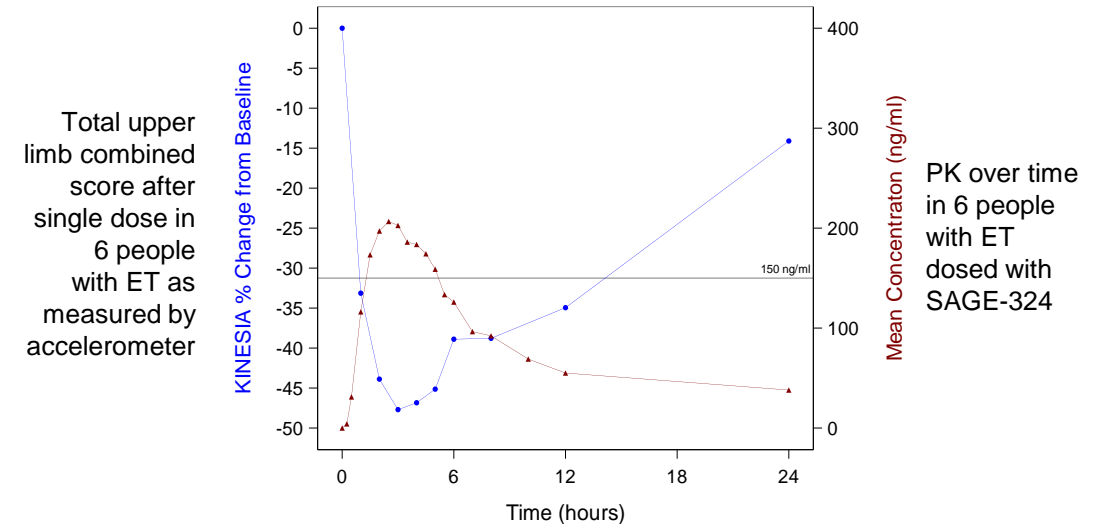
79% of employed patients have reduced hours or changed jobs due to ET

56% of patients require caregiving from family, friends, or professionals

SAGE-324: Novel potential treatment for movement disorders

Predictable PD effects and PK profile with long half-life

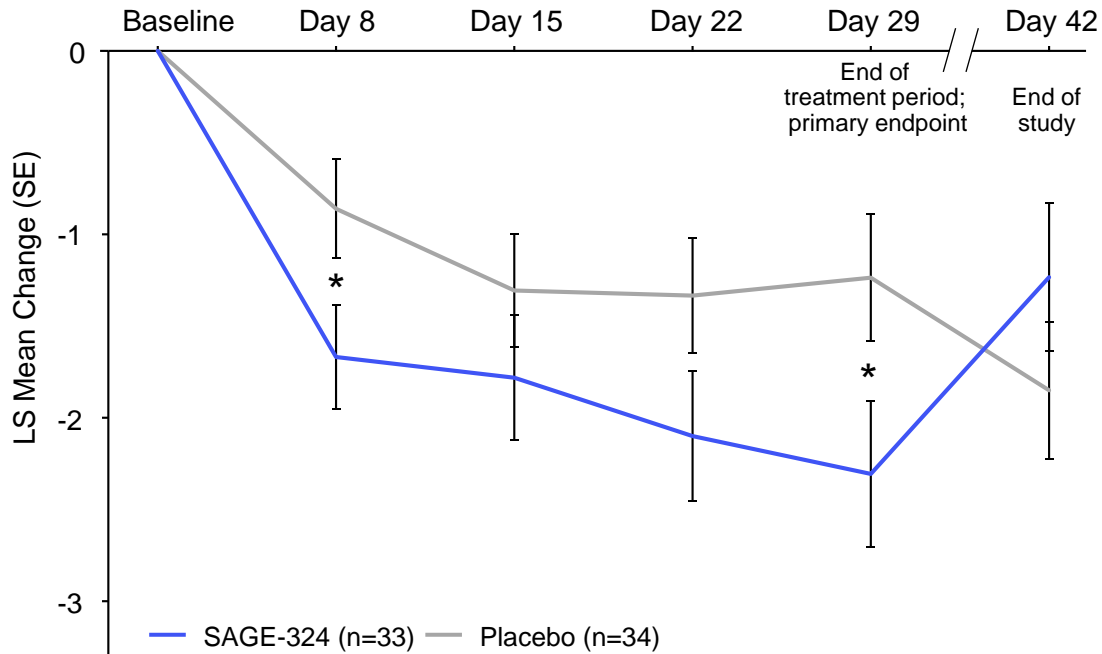
- SAGE-324 is well-suited for development in essential tremor (ET):
 - Most prevalent movement disorder in the US (est. 6M+)
 - Last pharmacological treatment for ET was approved in 1967
 - High unmet need; 50% of treated patients do not respond or have sub-optimal response to standard of care
- In an 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



- Clear PK/PD relationship
- Promising signals of tremor reduction, consistent with those observed previously for brexanolone and SAGE-217
- Most common AEs ($\geq 5\%$) included somnolence, dizziness, and feeling of relaxation

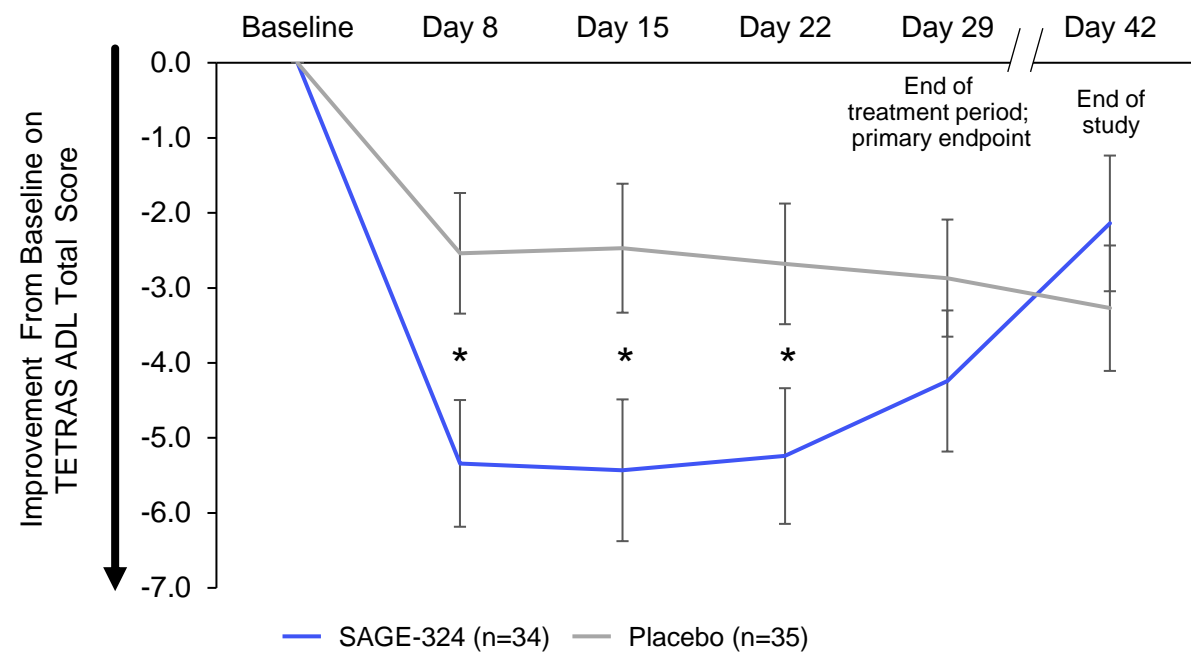
Improvement in tremor control and ADL score observed in the KINETIC Study

Change From Baseline for TETRAS Performance Subscale Upper Limb Tremor Total Score in SAGE-324 and Placebo Treatment Groups



Baseline mean (SD) TETRAS Performance Subscale Upper Limb Tremor Total Score: placebo 12.28 (1.69); SAGE-324 12.82 (1.73)

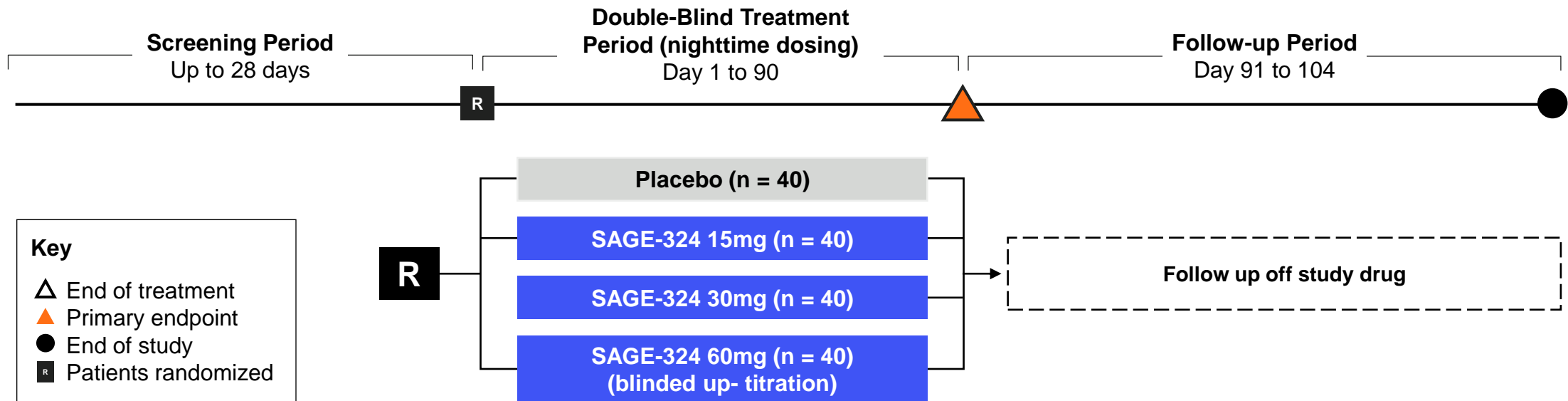
Change From Baseline for TETRAS ADL Subscale Total Score in SAGE-324 and Placebo Treatment Groups



Baseline mean (SD) TETRAS ADL Subscale Total Score: placebo 26.7 (6.84); SAGE-324 26.3 (8.50)

The most frequently reported adverse events reported by at least 10% of participants on SAGE-324 in the KINETIC Study were somnolence (68%), dizziness (38%), balance disorder (15%), fatigue (15%), diplopia (12%), dysarthria (12%), and gait disturbance (12%).

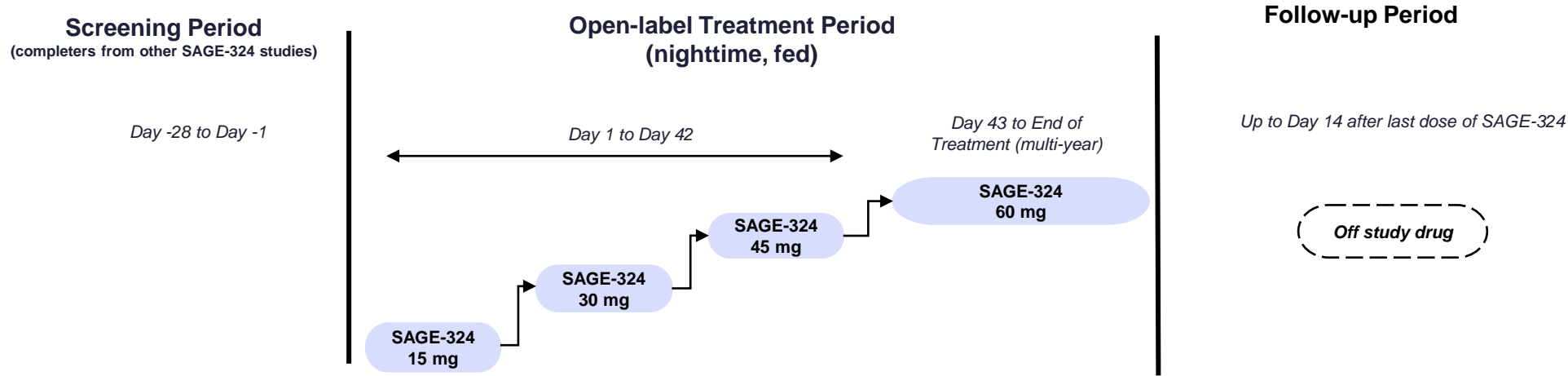
324-ETD-202: Phase 2 double-blind, randomized, placebo-controlled, dose-response study of SAGE-324 for the treatment of patients with essential tremor



- Patients with moderate to severe essential tremor
- Primary aim is to identify a dose-response
- Primary endpoint is change from baseline in TETRAS Performance Subscale Item 4 total score at Day 91
- Dose(s) selected for potential pivotal studies will balance efficacy with tolerability

SAGE-324 Long-Term Open Label Safety Study (ETD-303)

A Long-term, Open-Label Safety and Tolerability Study of SAGE-324 in Participants with Essential Tremor

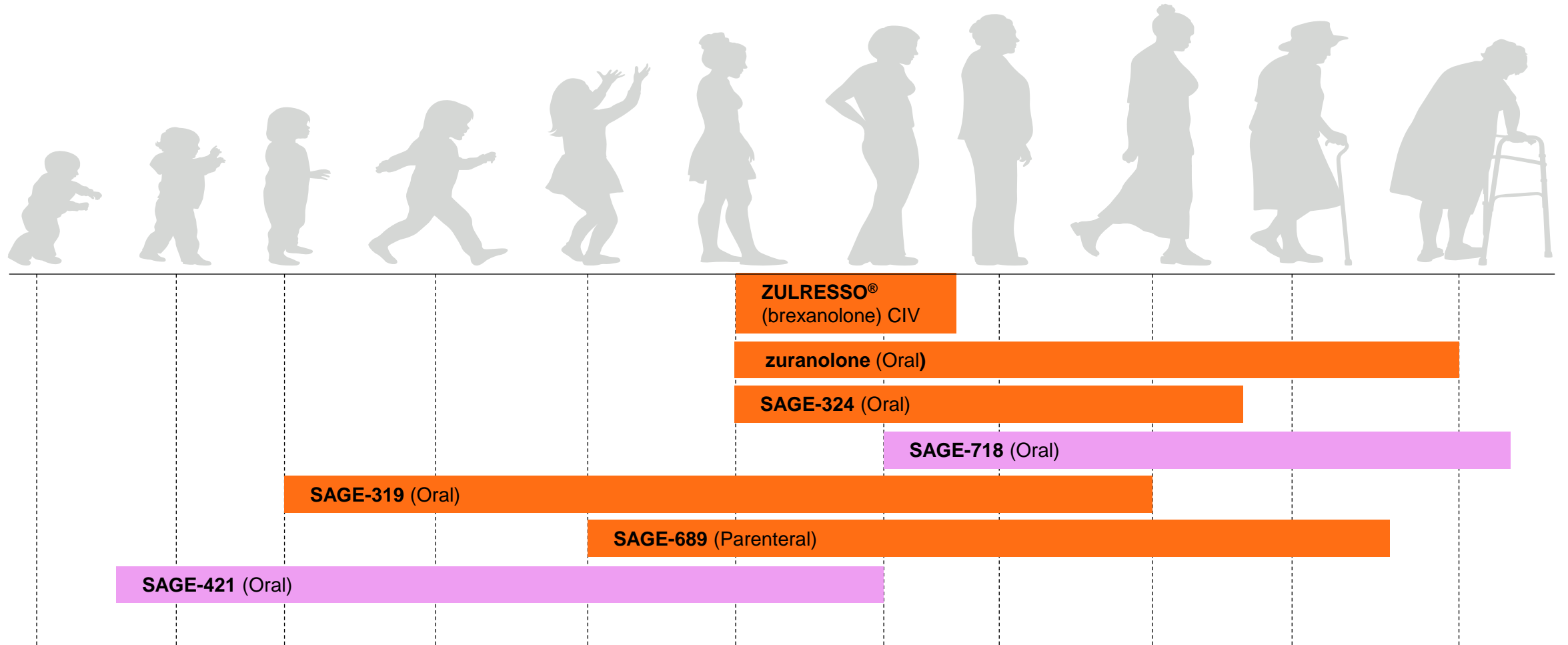


STUDY OVERVIEW

Status	Initiated	Objectives	<ul style="list-style-type: none"> To assess the long-term safety and tolerability of SAGE-324
Indication	Essential Tremor	Primary Endpoint	<ul style="list-style-type: none"> Incidence of treatment-emergent adverse events (TEAEs)
Phase	Phase 2	Key Secondary Endpoint	<ul style="list-style-type: none"> Change from baseline in vital signs, electrocardiogram (ECG) and clinical laboratory parameters, Epworth Sleepiness Scale (ESS), Physician Withdrawal Checklist (PWC-20), and Columbia-Suicide Severity Rating Scale (C-SSRS) responses
Arms	Open-label <ul style="list-style-type: none"> SAGE-324 	Inclusion Criteria	<ul style="list-style-type: none"> Be between the ages of 18 and 80 at Screening Participant has a clinician-confirmed diagnosis of ET in compliance with all the following criteria: <ol style="list-style-type: none"> Duration of at least 3 years Absence of other neurological signs, such as dystonia, ataxia, parkinsonism, task- and position-specific tremors, sudden tremor onset, or evidence of stepwise deterioration of tremor Absence of historical or clinical evidence of tremor with psychogenic origin Participant has successfully completed participation in another SAGE-324 study
Dosing Regimen	Up titration in 15mg increments to 60mg Nighttime, fed	Exclusion Criteria	<ul style="list-style-type: none"> Participant has presence of alcohol withdrawal state. Participant has had direct or indirect injury or trauma to the nervous system within 3 months before the onset of tremor. Participant is taking and unable to discontinue the use of primidone at least one month prior to administration of first dose of SAGE-324.

Sage proprietary product engine

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





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
- Planned 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



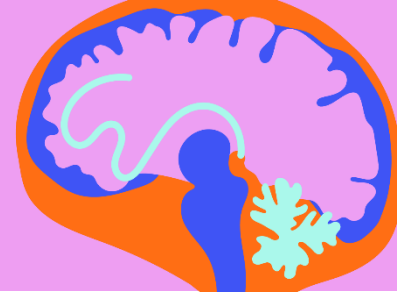
- Extra-synaptic GABA_A receptor preferring positive allosteric modulator
- Profile supporting daily, oral, chronic dosing
- Differentiated preclinical EEG signature compared to zuranolone and SAGE-324

Potential indications:

DISORDERS OF SOCIAL INTERACTION

Preclinical profile of SAGE-421

NMDA PAM



- NMDA receptor positive allosteric modulator
- Profile supporting daily, oral, chronic dosing

Potential indications:

NEURODEVELOPMENTAL DISORDER

First Quarter 2023 Financial Results

Strong financial position with \$1.1B in cash

Item	Q1 '23	Q1 '22
Revenue	\$3.3M	\$1.6M
R&D Expense	\$92.8M	\$78.0M
SG&A Expense	\$65.7M	\$46.5M
Cost of Goods Sold	\$0.2M	\$0.3M
Total Operating Costs and Expenses	\$158.8M	\$124.8M
Net Loss	(\$146.8M)	(\$122.1M)
Cash and Marketable Securities	\$1.1B	\$1.6B

Anticipated 2023 milestones

	Early	Mid	Late	
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 (August 5 th)
			●	Commercial availability of zuranolone in MDD and PPD, if zuranolone is approved with no review extensions
			●	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

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

Sage's goal is to become the leader in brain health

Fearlessly leading the way to create a world with better brain health

Rich data across programs sets up potential for long-term value creation through 2023 and beyond

Deep domain expertise paired with neuroactive steroid capability generating leading brain health pipeline

Progress five Phase 2 studies in 2023 and potential to receive approval on second marketed product

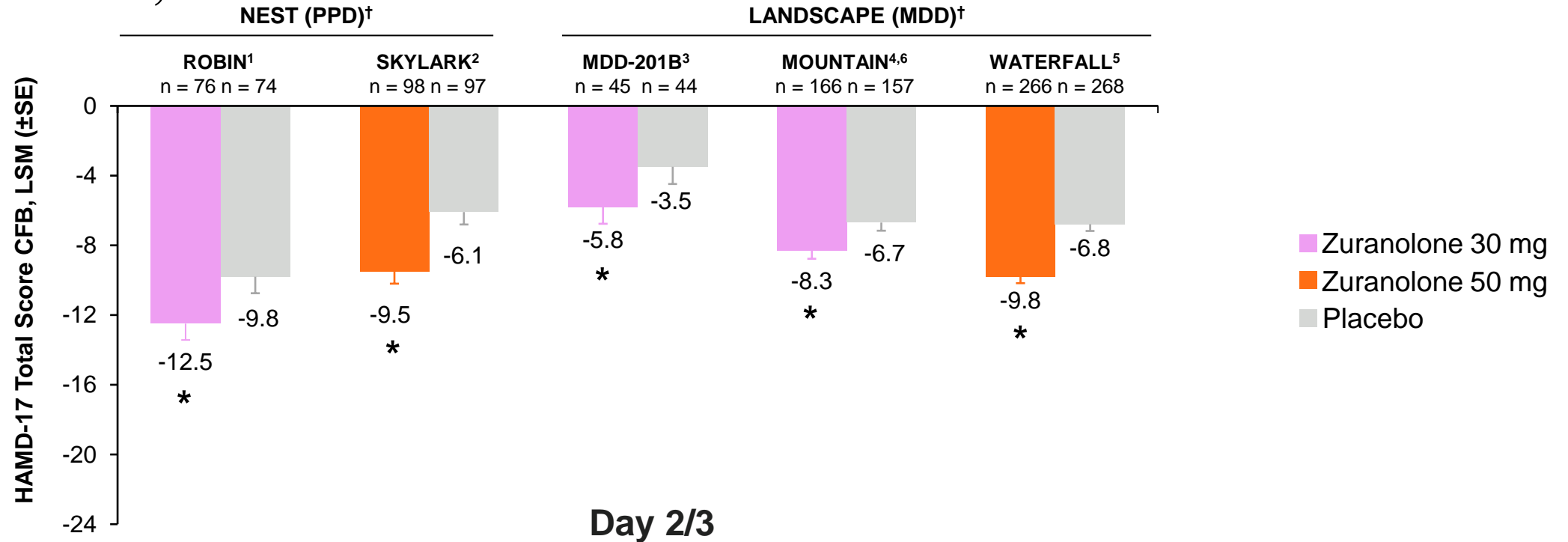
Focused on plans for potential commercialization of later-stage programs

Financial flexibility enables launch preparation and continued investment in innovation, with mission of creating top-tier biopharma in five years

Appendix

CFB in HAMD-17 Total Score at Day 2/3 in Placebo-controlled Trials

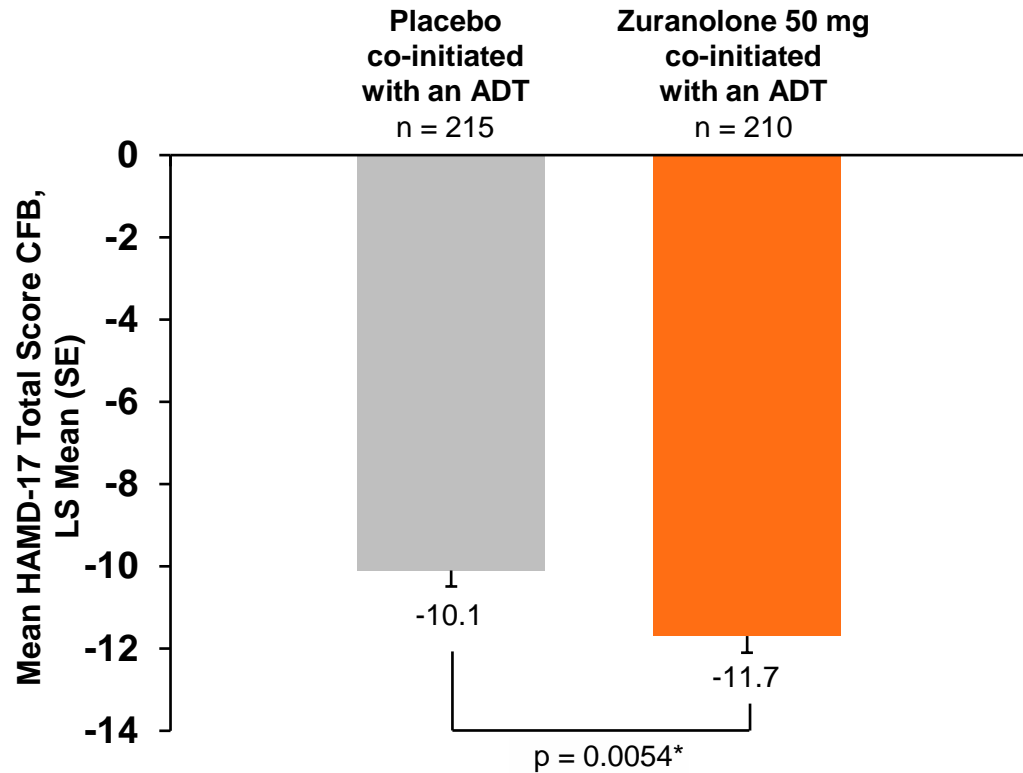
Numerical Improvement With Zuranolone vs Placebo at Day 2/3 in the ROBIN, SKYLARK, MDD-201B, MOUNTAIN, and WATERFALL Studies¹⁻⁵



The clinical trials above differ in sample size, patient population, entry criteria, and study sites as well as other design elements. No direct comparison can be made across these clinical trials based on the graph above. ROBIN and SKYLARK enrolled patients with PPD; MDD-201B, MOUNTAIN, and WATERFALL enrolled patients with MDD. Studies with Day 3 data: ROBIN, SKYLARK, MOUNTAIN, and WATERFALL; study with Day 2 data: MDD-201B.1-5

CORAL Study: Key secondary endpoint result

LS Mean CFB in HAMD-17 Total Score Using Equal Weights Over Days 3, 8, 12, and 15 (Blinded Treatment Period)^{1,2,†}
(Key Secondary Endpoint)



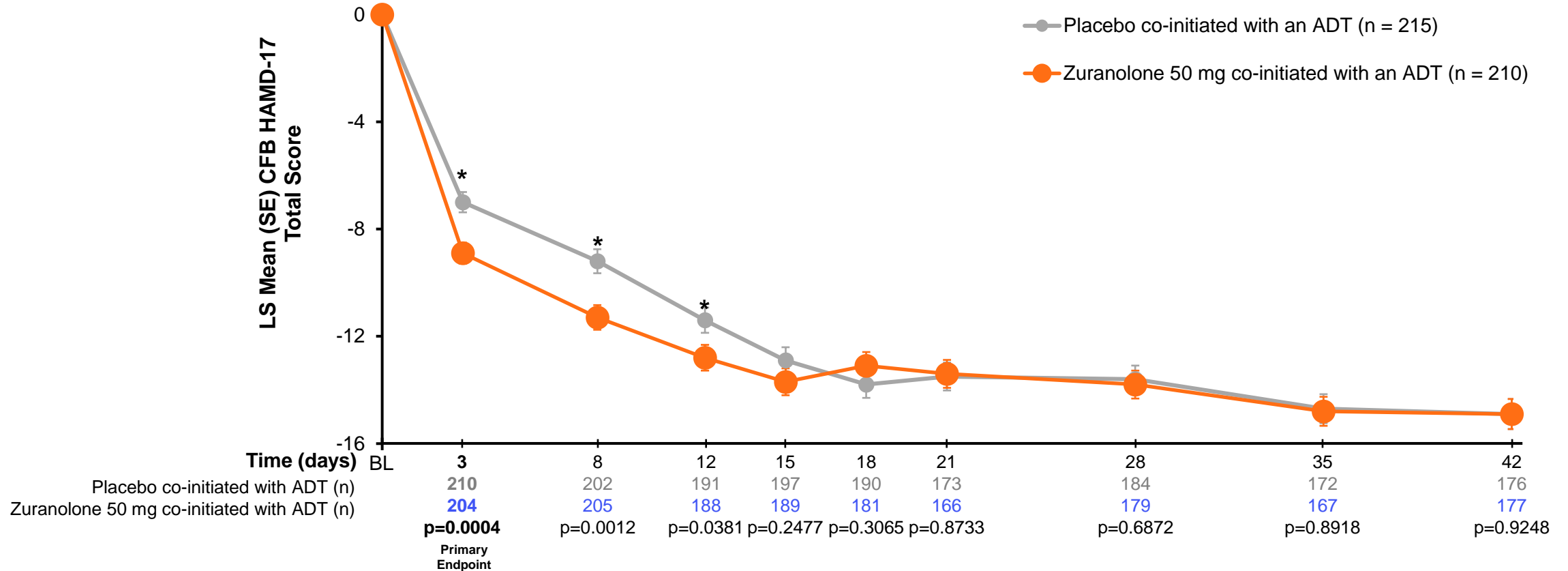
LS Mean CFB in HAMD-17 Total Score at Days 3, 8, 12, and 15 (Applied to Calculate the Key Secondary Endpoint)^{1,2}

Day	Placebo co-initiated with an ADT (n = 215)	Zuranolone 50 mg co-initiated with an ADT (n = 210)	p value [§]
	LS Mean HAMD-17 Total Score CFB	LS Mean HAMD-17 Total Score CFB	
3 [‡]	-7.0	-8.9	0.0004
8	-9.2	-11.3	0.0012
12	-11.4	-12.8	0.0381
15	-12.9	-13.7	0.2477

[§]p values for Days 8, 12, and 15 are nominal and not adjusted for multiplicity.

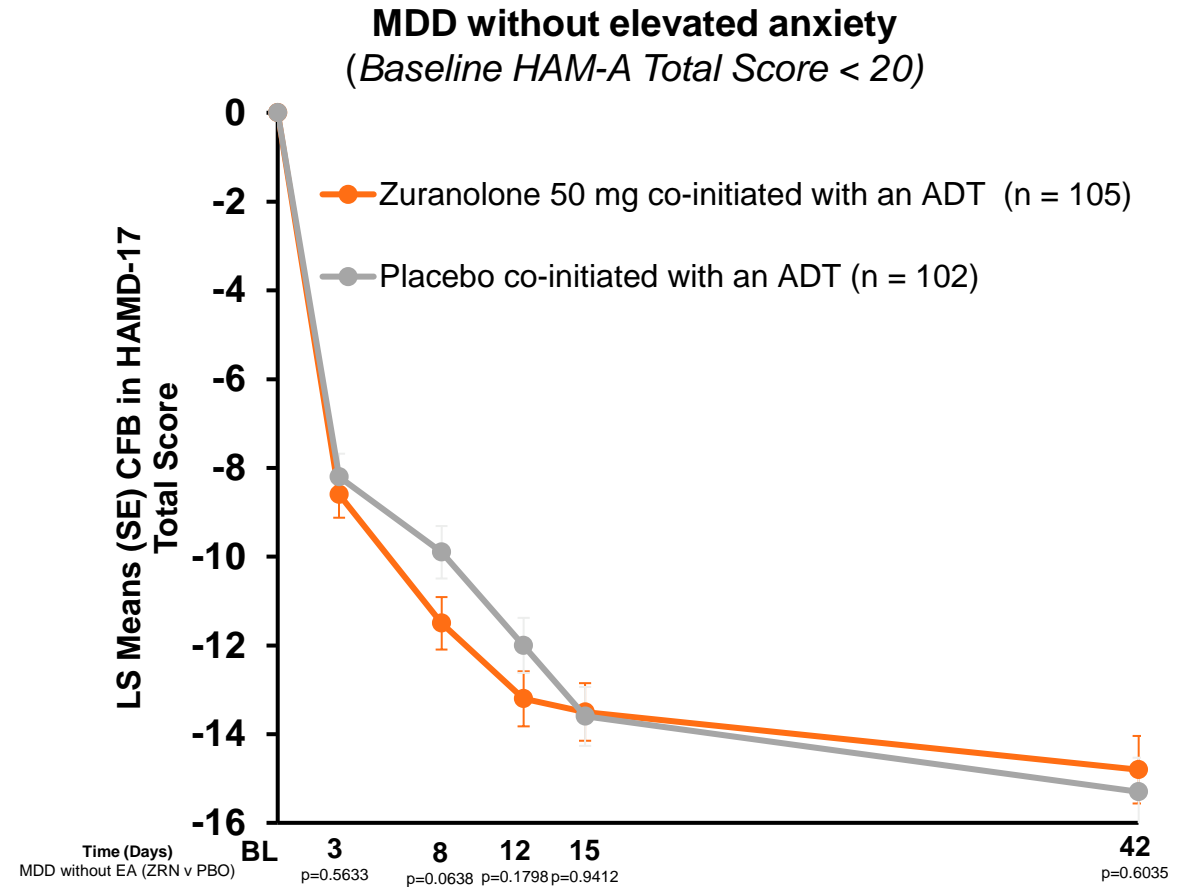
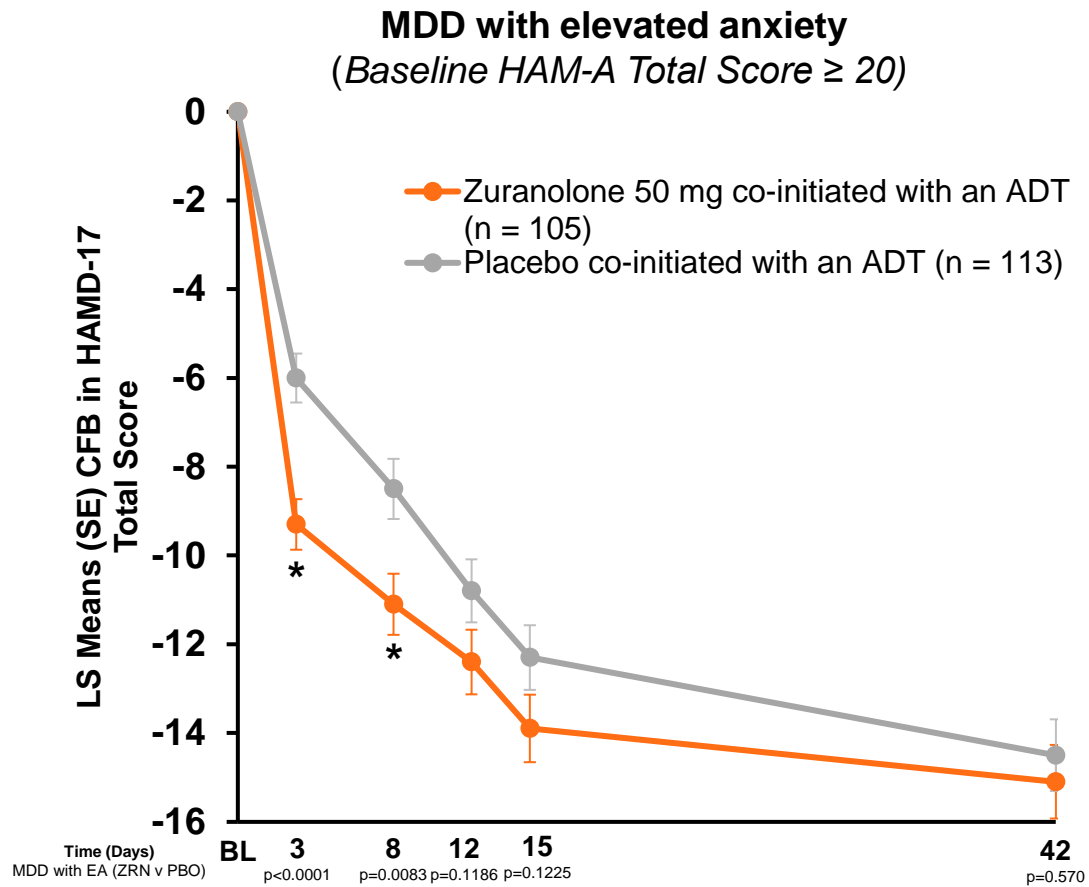
*The key secondary endpoint was statistically significant at a two-sided 0.05 level of significance under strong control of family-wise error rate.

CORAL Study: CFB in HAMD-17 Total Score at Each Time Point in the Study Period by Treatment Group (FAS)



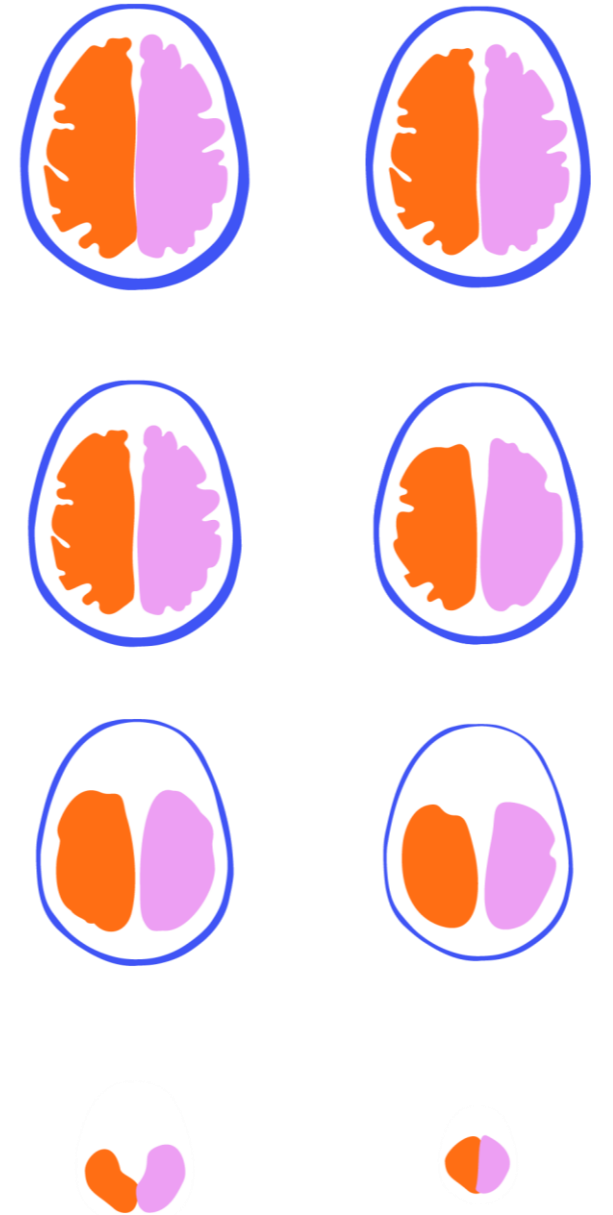
CORAL Study MDD with elevated anxiety as a key symptom of depression (baseline HAM-A ≥ 20)

LSM CFB HAMD-17 Total Score from Baseline Through Day 15



Proactive, predictive, productive and patient-focused drug development approach

- Sage is pairing deep GABA and NMDA domain expertise with leadership in neuroactive steroids
 - >8K compound library and >800 issued patents and patent applications globally
- Focus on understanding how to modify circuitry that impacts brain function at the network level
- Robust engine for turning early ideas rapidly into clinical proof-of-concept
- Dedicated to improving patients' lives by focusing on the things that matter most to them



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

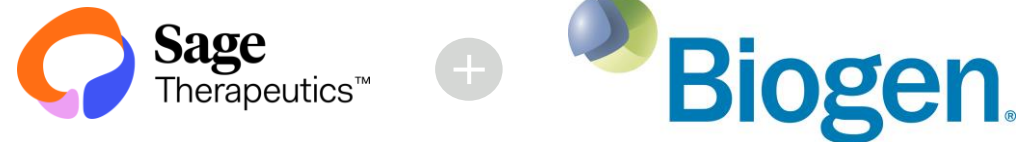
Upfront payment

\$485M

Potential development & commercial milestones

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



\$1.5B

Upfront payment and equity investment

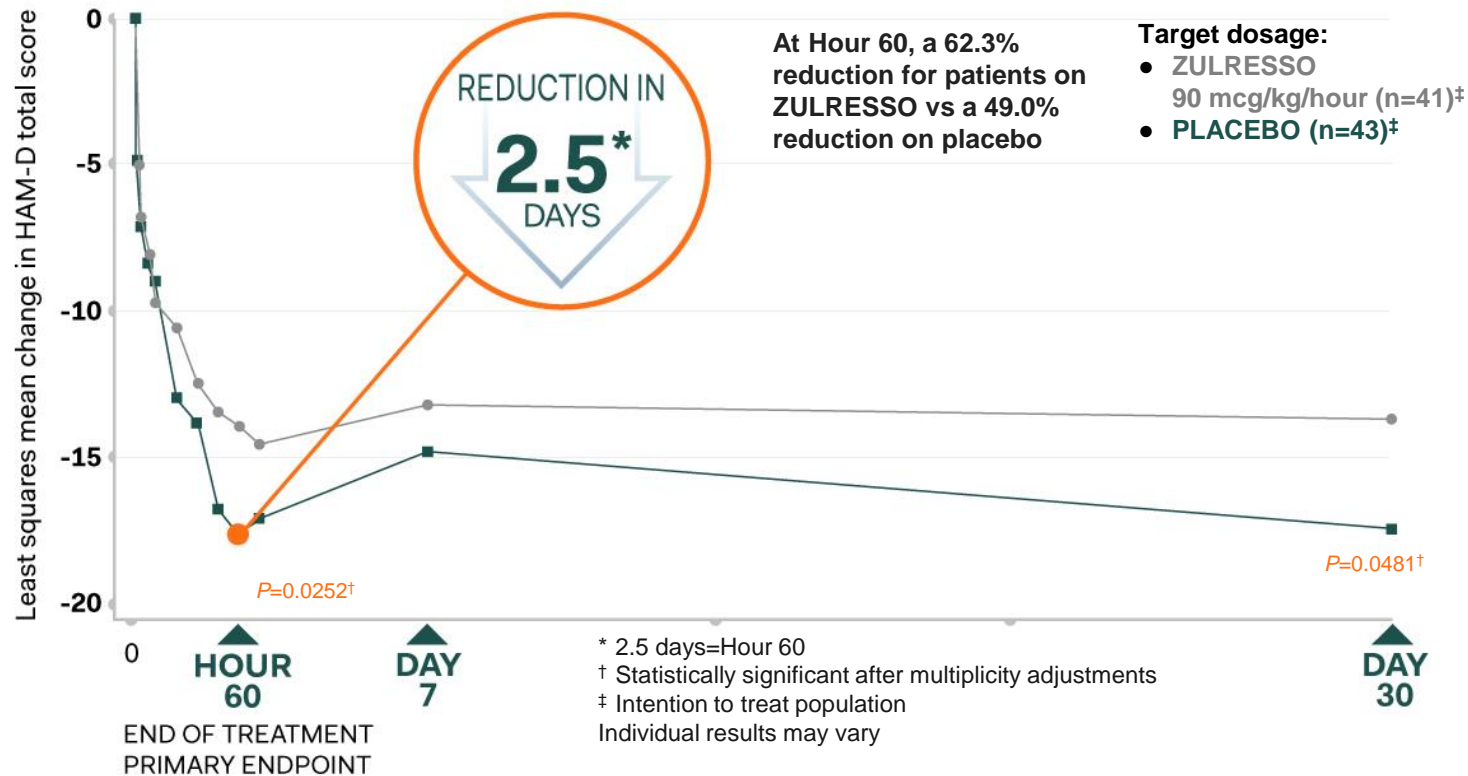
\$1.6B

Potential development & commercial milestones

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 30ⁱ

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 REMSⁱⁱⁱ

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.



Seeing the
brain differently
*makes a world
of difference*