Sage Therapeutics®

Investor Presentation

November 2022

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 initiation and completion of trials and reporting of results; the expected timeline for completion of the NDA filing for zuranolone in MDD and PPD; our belief that we have sufficient data to support filing and approval of the NDA for zuranolone; the potential for priority review of the zuranolone NDA; the potential for approval of zuranolone in MDD and PPD, including expected timelines for review of the NDA and launch of zuranolone, if approved; our belief in the potential benefit and profile for zuranolone and in its potential to be successful and to be an advance in the treatment of MDD and PPD; the potential for successful commercialization of zuranolone, if approved, including our plans, strategies and expectations for go-to-market strategies, market acceptance and use and reimbursement; 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 and uses for zuranolone and our other product candidates, if approved; the goals, opportunity, mission and vision for our Company and potential for our business; our views with respect to potential value creation opportunities; the potential benefits and results that may be achieved through our collaborations with Biogen and Shionogi; our plans for advancing, accelerating and expanding our development efforts and the output of our research engine; our belief in the potential for upcoming catalysts and milestones to support our mission and goals; our expectations with respect to year-end cash, future expense increases and future funding of operations; and our belief in our ability to achieve our mission and to become the leading brain health company and top-tier pharmaceutical company with multiple franchises.
- These forward-looking statements are neither promises nor guarantees of future performance, and are subject to a variety of risks and uncertainties, many of which are beyond our control, which could cause actual results to differ materially from those contemplated in these forward-looking statements, including the risk that:
  - We may not meet our expected time-lines with respect to the NDA filing for zuranolone. The FDA may not accept our NDA for review or may accept the filing for review but not grant approval. 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.
  - Our clinical trials may not meet their primary endpoints or key secondary endpoints. Success in non-clinical studies or in prior clinical trials of our product candidates may not be repeated or observed in ongoing, planned or future studies involving the same compound or other product candidates. Final results of studies where we reported interim results may not be consistent with the interim results. Non-clinical and clinical results from ongoing or future trials may not support further development of the product candidate or 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.
  - Shortages of personnel at clinical sites and vendors, whether related to the COVID-19 pandemic or as a result of the post-pandemic economic environment, may have a more significant impact on our clinical development timelines, data or business than we expect.
  - At any stage, 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. 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.
  - 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;
  - We may never achieve the rate of new product candidates from our research engine that we expect in the future.
  - Even if our products are successfully developed and approved, the number of patients with the diseases or disorders our products treat, the unmet need for new treatment options, the benefit of our products and the actual market for such products may be smaller than our current estimates; or we may not achieve market acceptance or reimbursement at acceptable levels. Our product may ultimately be approved for only a subset of patients with the diseases we studied or may be used in only a portion of the patients within the approved indication. We may never be successful or achieve our goals with respect to commercialization of zuranolone, even if approved, or any of our other product candidates that may be approved in the future;
  - 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 its products, or to defend ours patent portfolio against challenges from third parties.
  - We may face competition from others developing products for similar uses as those for which our product candidates are being developed.
  - Our operating expenses may be higher than forecasted, and we may also face unexpected expenditures which could cause us to change our plans, and as a result, our expectations as to year-end cash or funding for future operations may prove not to be correct.
  - We may not be able to establish and maintain key business relationships with third parties or we may encounter technical and other unexpected hurdles in the manufacture and development of our products.
  - Any of the foregoing or other factors may negatively impact our ability to achieve our goals, mission, opportunities, plans or expectations for our business.
- For additional disclosure regarding these and other risks Sage faces, see the disclosure contained in the "Risk Factors" section of our most recent report, and in our other public filings, with the Securities and Exchange Commission, available on the SEC's website at http://www.sec.gov. Any forward-looking statement represent our views only as of today, and should not be relied upon as representing our views as of any subsequent date. We undertake no obligation to update or revise the information contained in this presentation, whether as a result of new information, future events or circumstances or otherwise.

Sage's vision is to fearlessly lead the way to create a world with better brain health

- Expertise in brain circuitry
- Rich pipeline across 3 franchises
  - First and only product approved specifically for postpartum depression
  - 3 late-stage programs
  - 6 clinical phase NCE development programs across 11+ potential indications
  - Strong intellectual property strategy
- Product platform to drive goals for ongoing growth
- $1.4B capital (as of 9/30/22) and collaborations to fund efforts to accelerate and advance medicines
- Potential to impact an estimated >450M patients globally

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Pipeline: Advancing a leading brain health portfolio

Compound	Partners	Indications	Preclinical	Phase 1	Phase 2	Phase 3	Registration	Marketed
DEPRESSION FRANCHISE								
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 FRANCHISE								
SAGE-324	Biogen	Essential Tremor						
		Epileptiform Disorders						
		Parkinson's Disease						
SAGE-689		Acute GABA Hypofunction						
NEUROPSYCHIATRY FRANCHISE								
SAGE-718		Huntington's Disease Cognitive Dysfunction						
		Parkinson's Disease Cognitive Dysfunction						
		Alzheimer's Disease Mild Cognitive Impairment and Mild Dementia						
ADDITIONAL CLINICAL PROGRAMS								
SAGE-421		NMDA Hypofunction						
SAGE-319		GABA Hypofunction						

**Rolling submission of NDA in MDD and PPD initiated with FDA, which we expect to complete in 2H22*

--- indicates trials in the planning or evaluation stage

Depression Franchise

Paucity of innovation plagues MDD disease landscape

- Prevalence and impact continue to increase globally
  - 62% of MDD respondents in the U.S. were severely impaired by their depression in a survey conducted by the World Health Organization[1]
  - Depression has generational impact as well as direct impact on caregivers (e.g., caregivers/partners unable to work full time, increasing economic burden exponentially)
- MDD may present in various phenotypes, such as MDD with elevated anxiety
  - MDD with elevated anxiety is known to be associated with poorer short- and long-term outcomes in relation to SSRI/SNRI pharmacotherapy[2]
  - PPD often presents with elevated anxiety as a symptom[3]

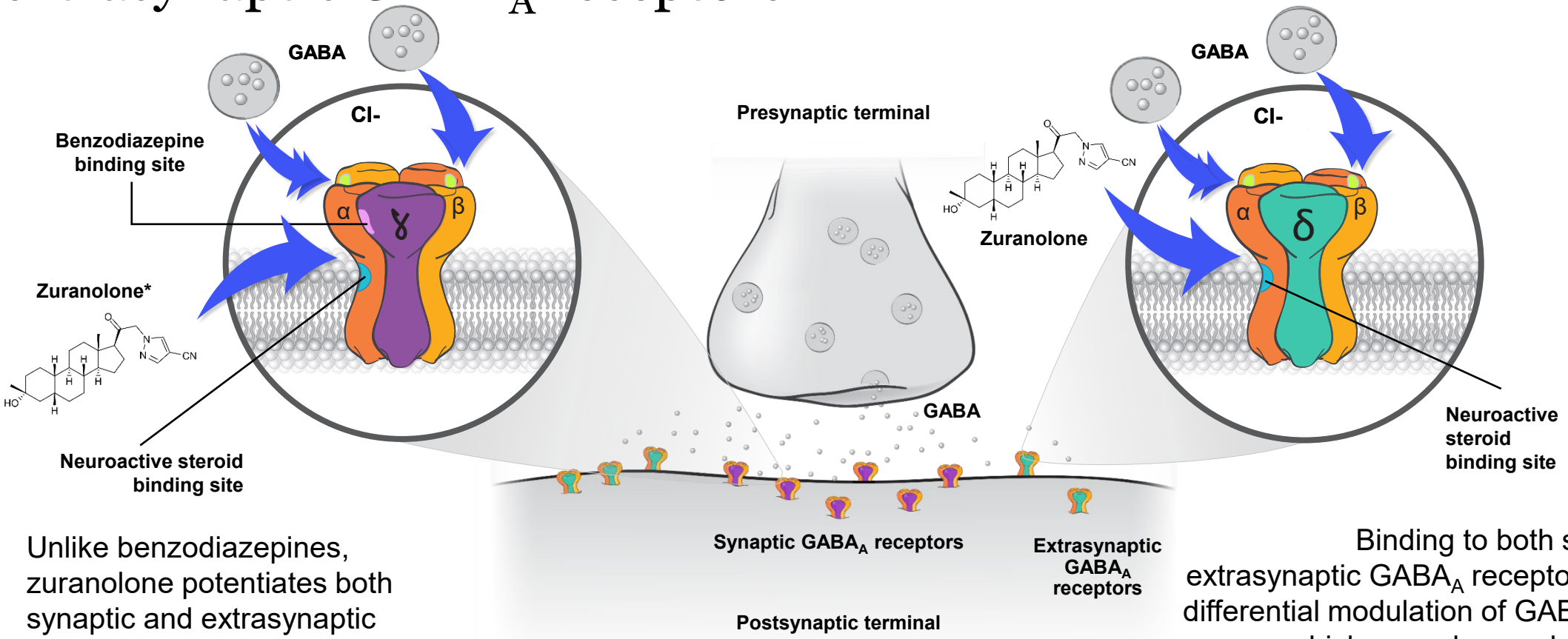
In a survey of MDD patients conducted by Sage:

68% reported that they were not satisfied with the amount of time they take medication[4]

75% reported being frustrated with the need to switch and try multiple options to treat their MDD[4]

[1]Bromet 2018
[2]Wu et al., 2013; Papakostas et al., 2008; Souery et al., 2007; Fava et al., 2006; Fava et al, 1997; Fava et al 2008; Ionescu et al, 2013, 2014; Papakostas et al, 2011
[3]Fairbrother N, Janssen P, Antony MM, et al. *J Affect Disord*. 2016;200:148-155; Postpartum Depression: Action Towards Causes and Treatment (PACT) Consortium. *Lancet Psychiatry*. 2015;2(1):59-67
[4]Sage Therapeutics, Inc. Data on file.

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 vitro[3]

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 brain[3]

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

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*Allopregnanolone has a similar pharmacology to zuranolone.

1. Jacob TC et al. *Nature Rev Neurosci.* 2008;9:331-343. 2. Reddy DS et al. *Trends Pharmacol Sci.* 2016;37:543-561. 3. Martinez Botella GM et al. *J Med Chem.* 2017;60:78109-7819.

Zuranolone is being developed in collaboration with Biogen.

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

Rapid & Sustained

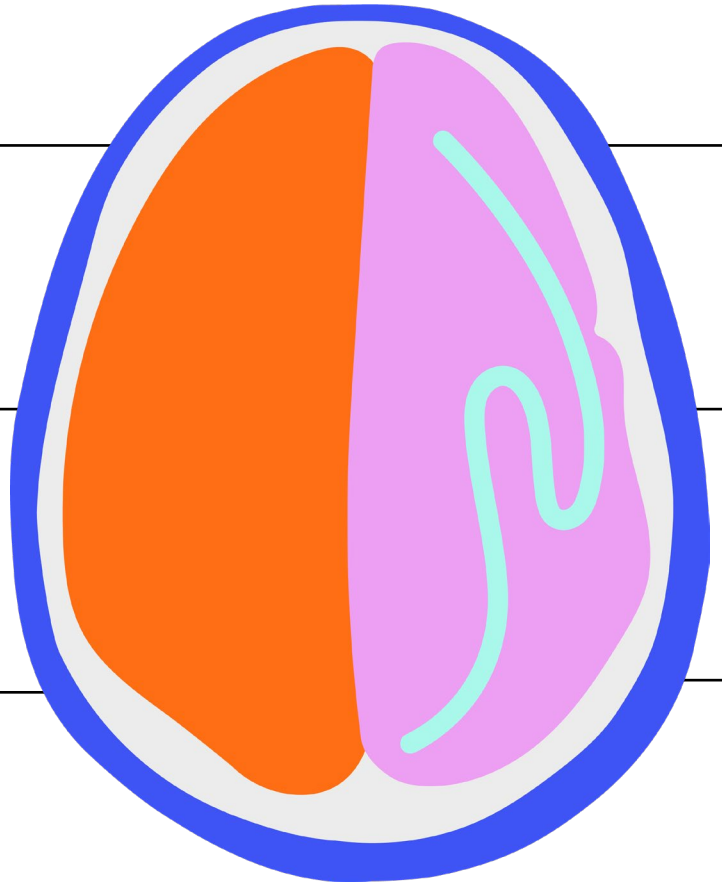
- Rapid symptom reduction
- Sustained effects lasted beyond completion of treatment

Well-Tolerated

- Favorable tolerability profile
- Differentiated side effect profile with no sexual dysfunction, weight gain or sleep disruption

Improved Feel/Functioning

- Improvements across domains of quality of life
- 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

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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).

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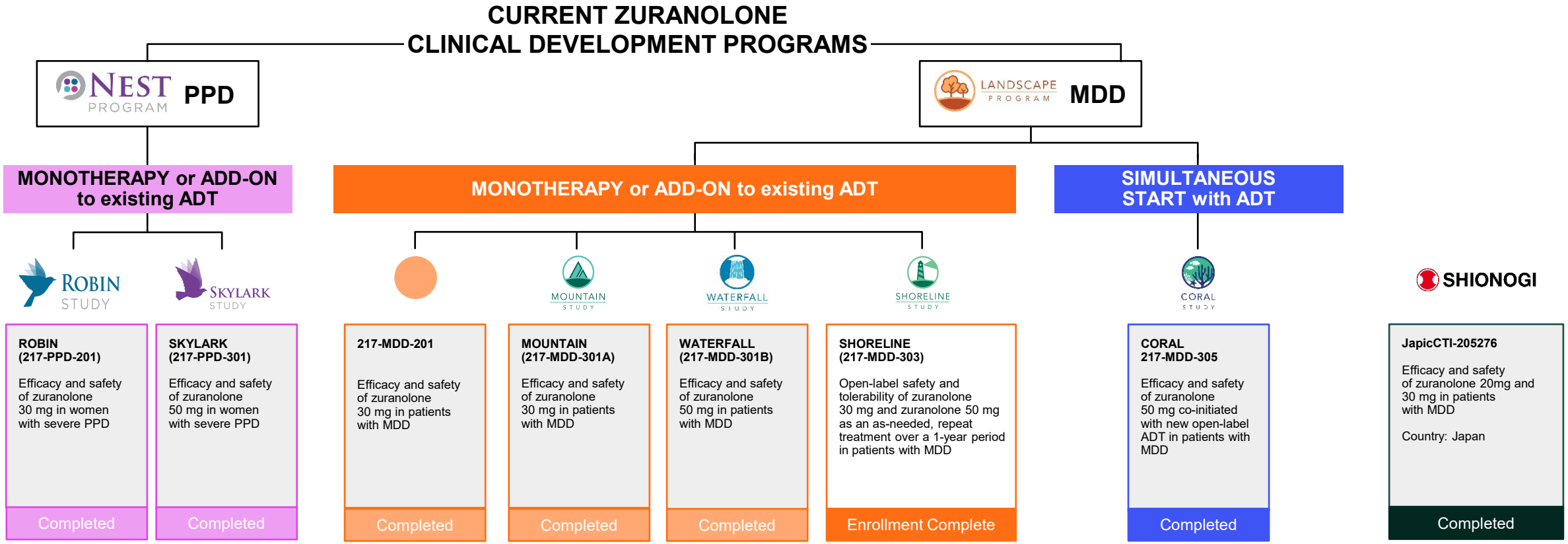
Zuranolone Clinical Development Programs

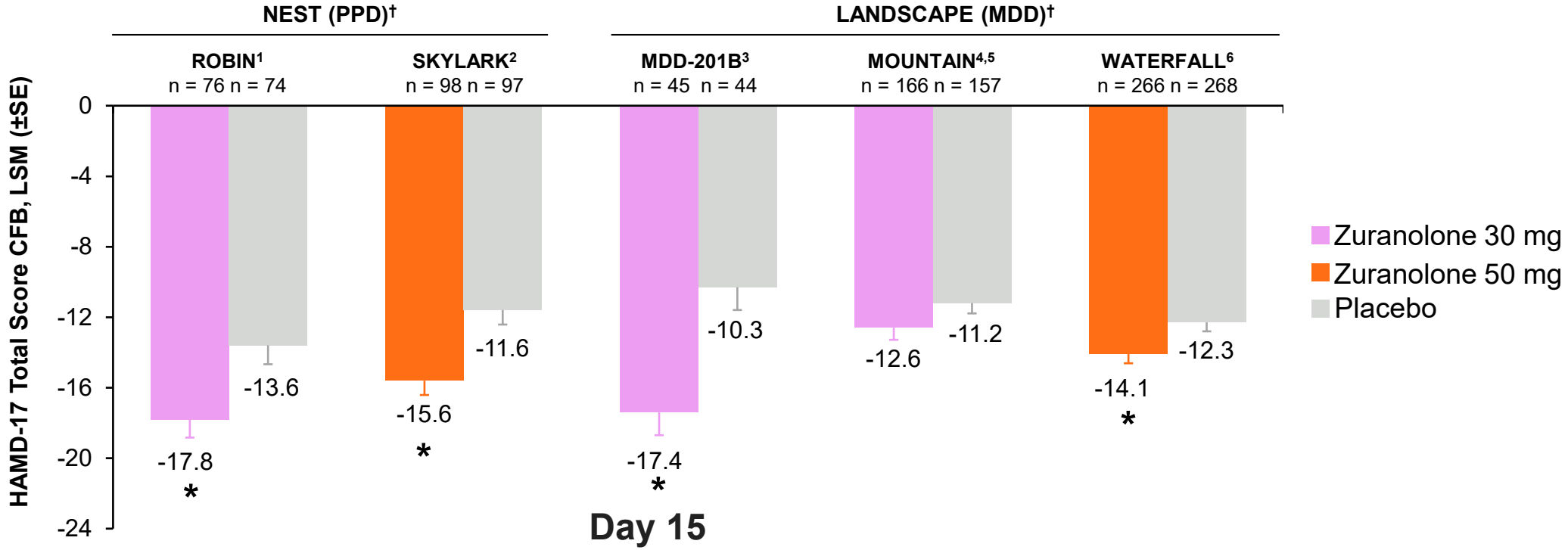
Potential to reshape the depression landscape



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

CFB in HAMD-17 Total Score at Day 15 in Placebo-controlled Trials

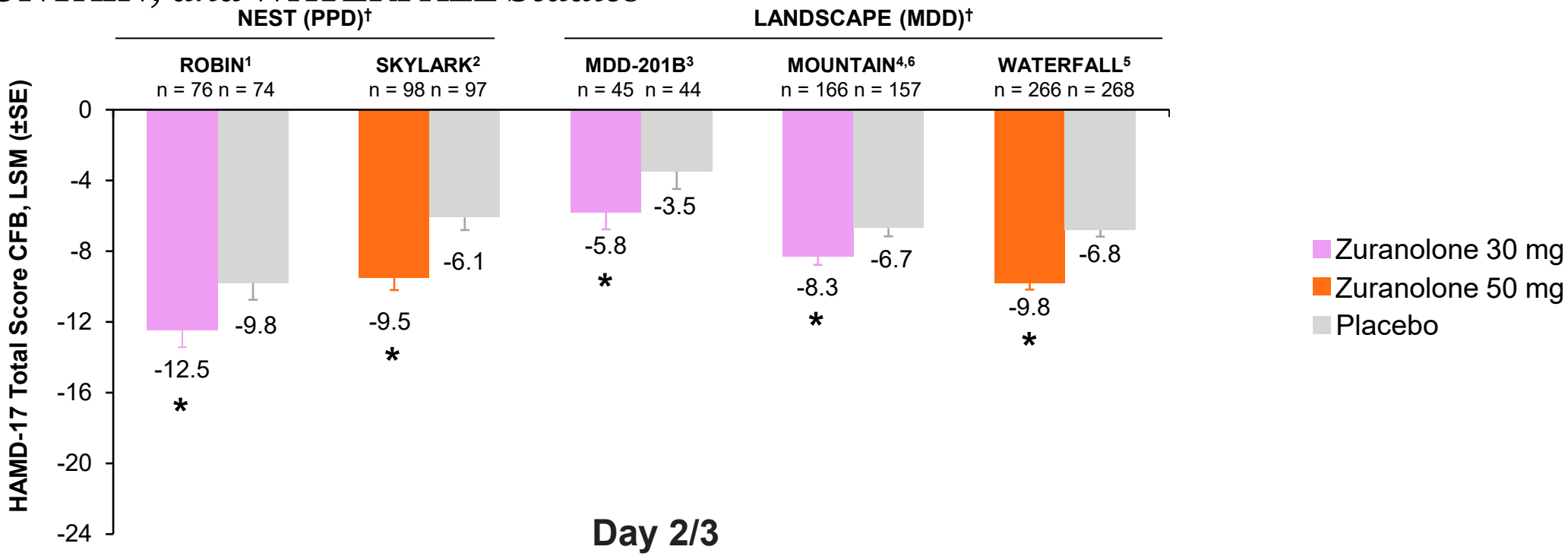
Statistically Significant Improvement with Zuranolone vs Placebo at Day 15 (Primary Endpoint) in the ROBIN, SKYLARK, MDD-201B, and WATERFALL Studies[1-6]



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.1-4,6

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 Studies[1-5]



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

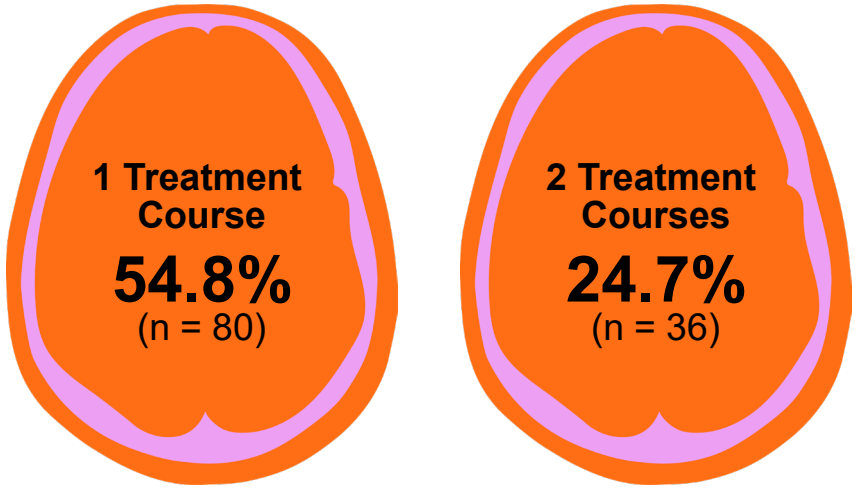
Zuranolone demonstrated sustained effects in the SHORELINE Study

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

GABA PAM

50 mg*

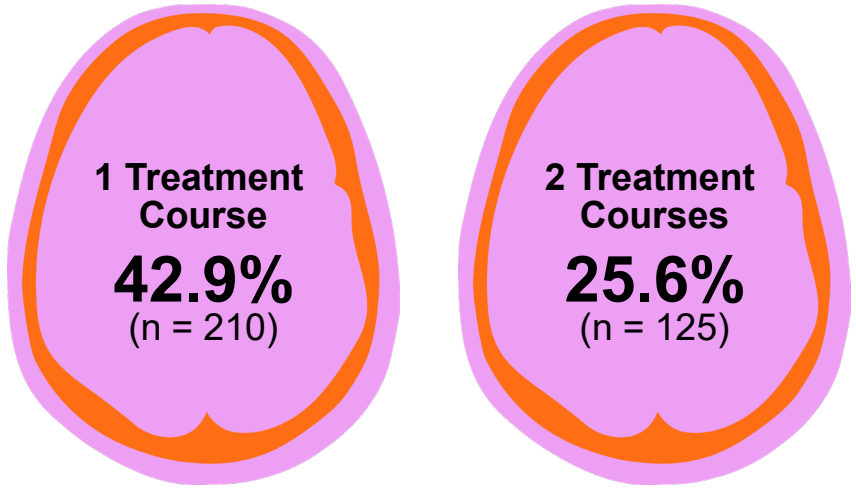
~80% of patients who responded to initial course received 1 or 2 treatment courses



3 Treatment Courses	4 Treatment Courses	5 Treatment Courses
10.3% (n = 15)	6.8% (n = 10)	3.4% (n = 5)

30 mg*

~70% of patients who responded to initial course received 1 or 2 treatment courses



3 Treatment Courses	4 Treatment Courses	5 Treatment Courses
11.9% (n = 58)	10.8% (n = 53)	8.8% (n = 43)

- 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 median time (95% CI) to Treatment Course 2 in the zuranolone 50 mg cohort was 249 (184, NE) days.[2]
- The SHORELINE Study was designed to evaluate efficacy in an observational manner, and therefore, statistical inferences cannot be drawn from efficacy outcome data.[3]

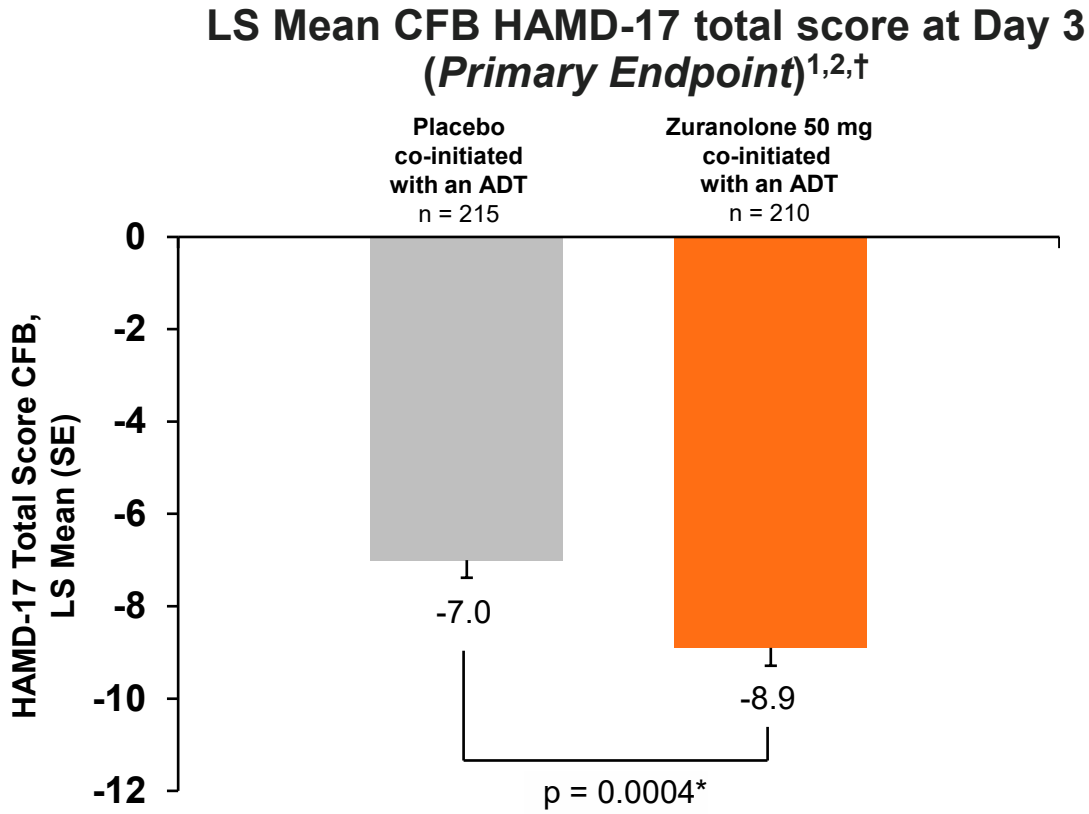
Only responders (≥50% reduction in HAMD-17 total score from baseline) at Day 15 of the initial treatment period can continue in the SHORELINE Study.

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). †De 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. Cutler AJ et al. Presented at American Society of Clinical Psychopharmacology Annual Meeting; May 31 – June 3, 2022. 3. Cutler AJ et al. Presented at Society of Biological Psychiatry Annual Meeting, 2021 Virtual Meeting; April 29-May 1, 2021.

Zuranolone is being developed in collaboration with Biogen.

CORAL Study: Day 3 primary endpoint result



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

†n values are based on the Full Analysis Set (FAS), defined as all randomized patients administered blinded zuranolone 50 mg or placebo with a valid baseline and at least 1 valid post-baseline efficacy endpoint.
ADT = antidepressant therapy; CFB = change from baseline; HAMD-17 = 17-item Hamilton Rating Scale for Depression; LSM = least squares mean; SE = standard error.

1. Parikh, SV. et al. Presented at American Society of Clinical Psychopharmacology Annual Meeting; May 31 – June 3, 2022

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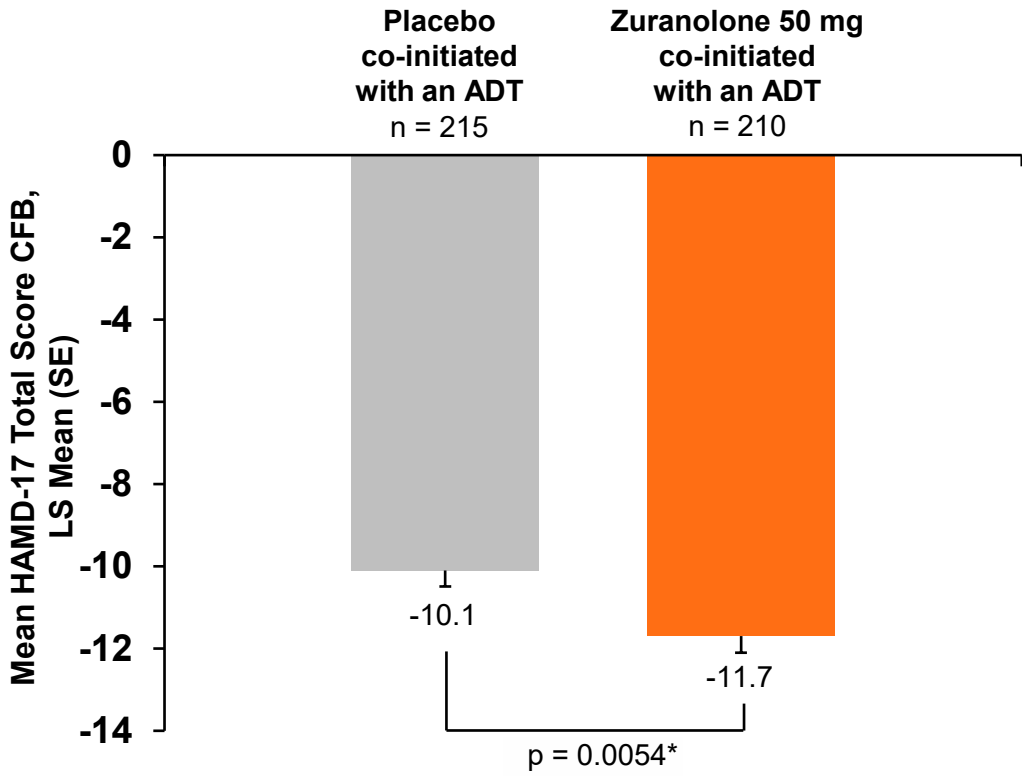
CORAL Study: Key secondary endpoint result

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*)



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

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) LS Mean HAMD-17 Total Score CFB	Zuranolone 50 mg co-initiated with an ADT (n = 210) LS Mean HAMD-17 Total Score CFB	p value[§]
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.

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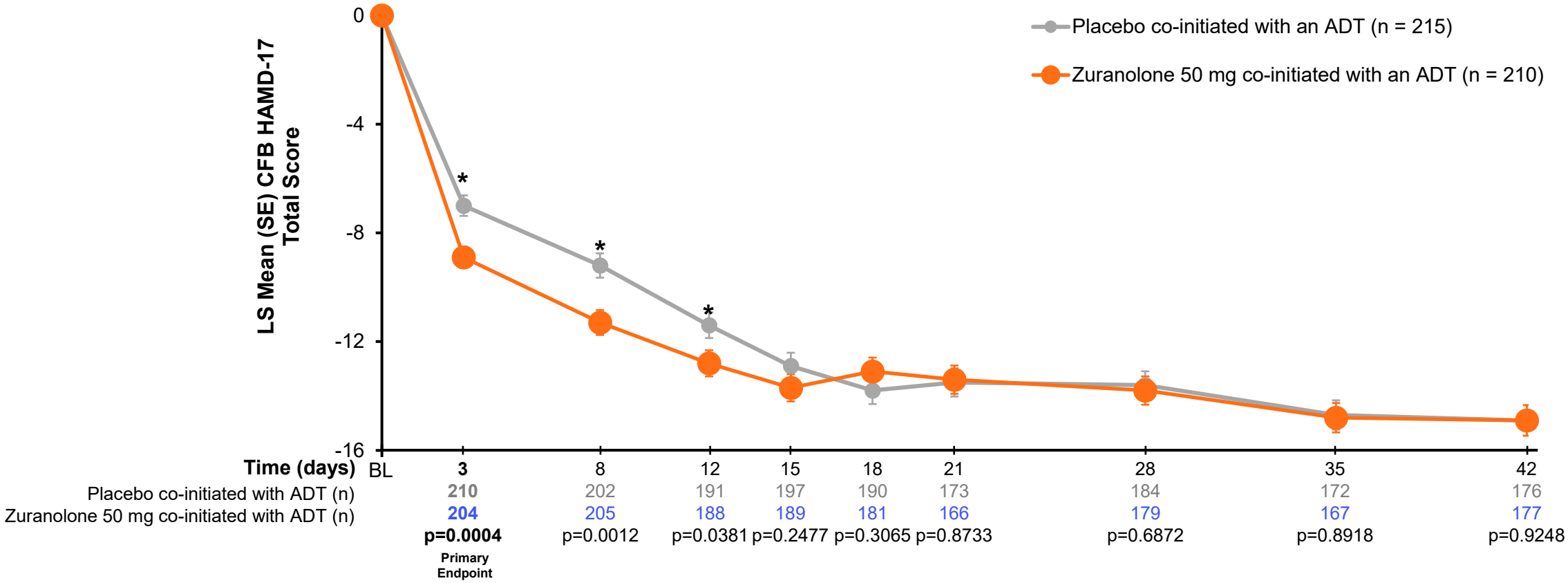
CORAL Study: CFB in HAMD-17 Total Score at Each Time Point in the Study Period by Treatment Group (FAS)



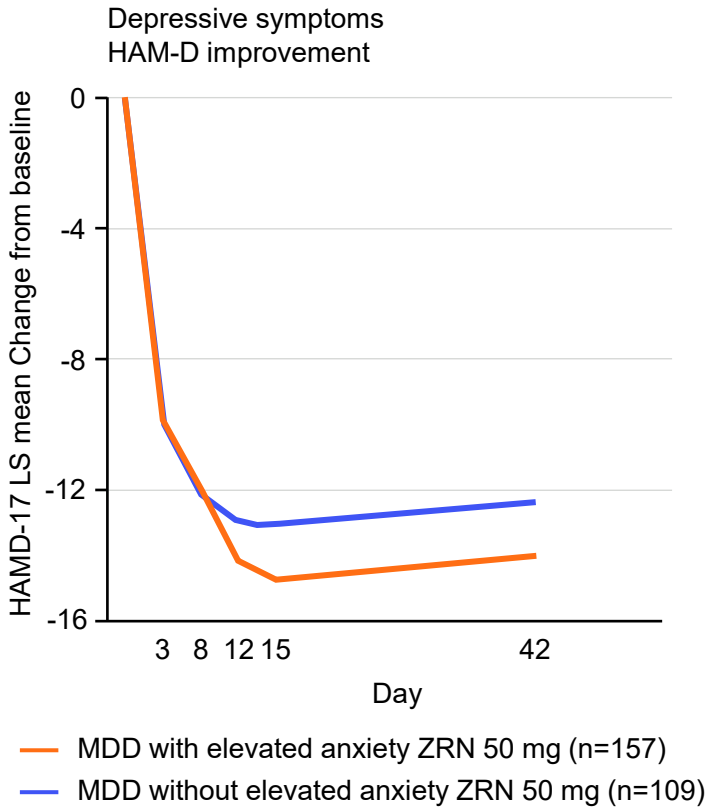
Parikh, SV. et al. Presented at American Society of Clinical Psychopharmacology Annual Meeting; May 31 – June 3, 2022

Zuranolone is being developed in collaboration with Biogen.

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., HAMD-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



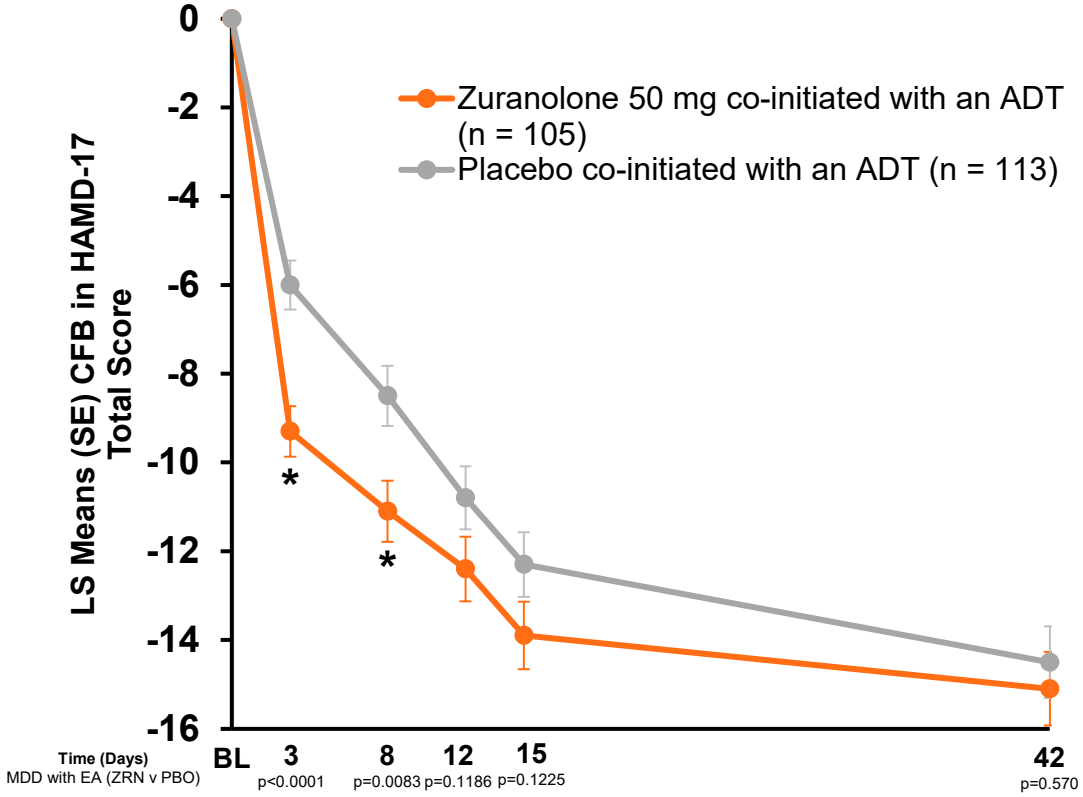
Fava et al, 1997; Fava et al, 2006; Fava et al 2008; Ionescu et al, 2013, 2014; Papakostas et al, 2011
MDD with elevated anxiety is defined as a person with MDD who has a baseline HAM-A ≥20

Zuranolone is being developed in collaboration with Biogen.

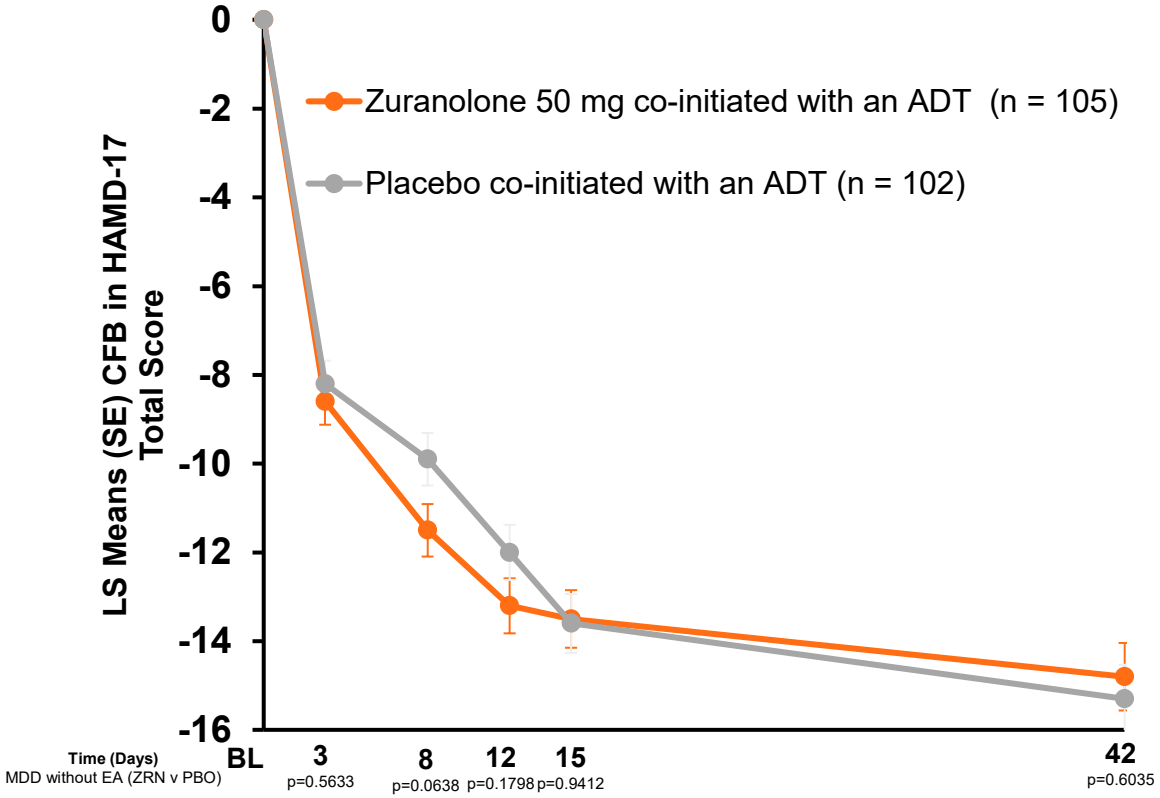
CORAL Study MDD with elevated anxiety as a key symptom of depression (baseline HAM-A ≥ 20)

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

MDD with elevated anxiety
(*Baseline HAM-A Total Score ≥ 20*)



MDD without elevated anxiety
(*Baseline HAM-A Total Score < 20*)



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Parikh, SV. et al. Presented at American Society of Clinical Psychopharmacology Annual Meeting; May 31 – June 3, 2022

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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-being[2]
- 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

Mental Health

Vitality	Social Functioning	Role Emotional	Mental Health

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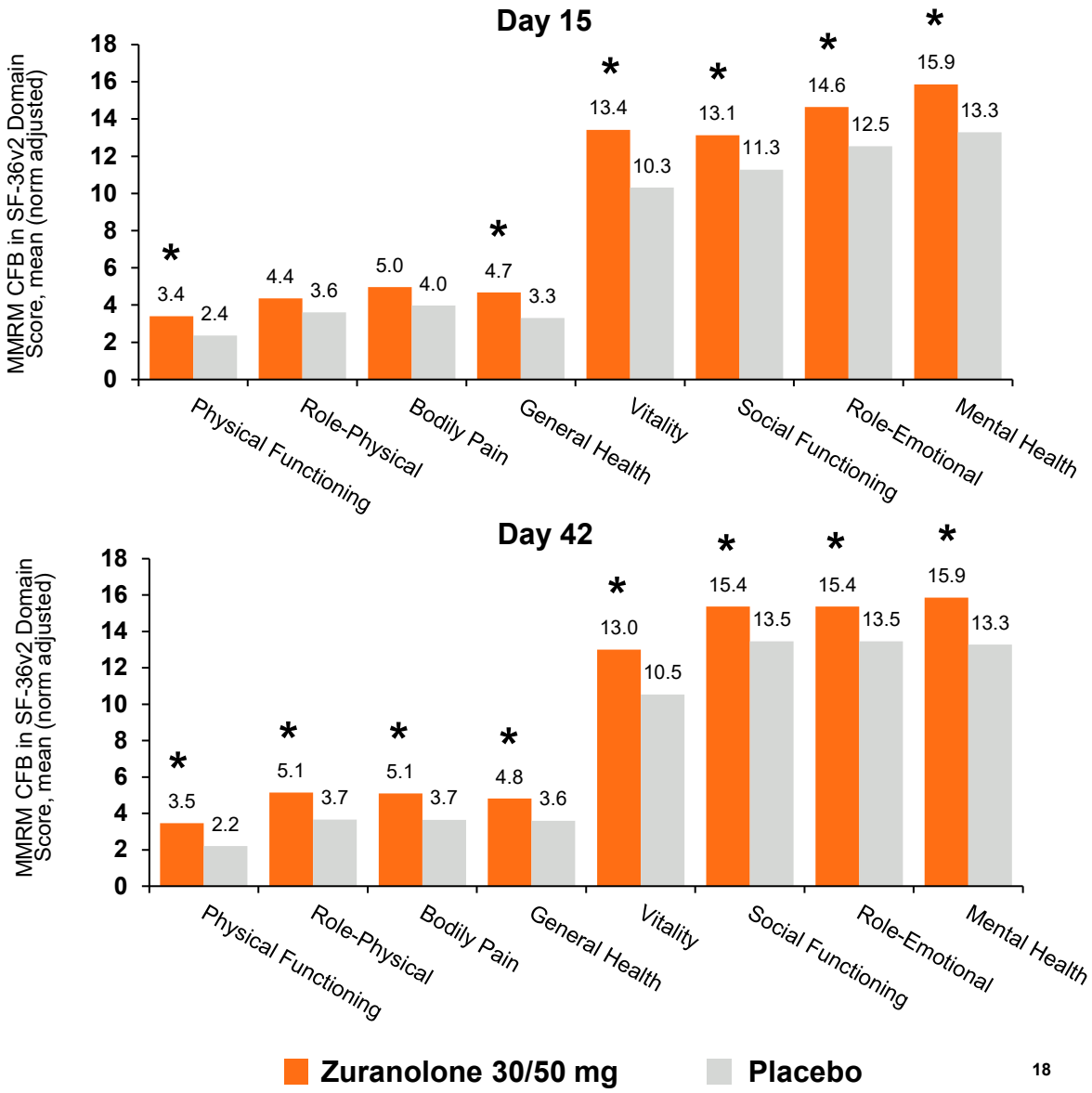
1. Maruish, M. E. (Ed.). User's manual for the SF-36v2 Health Survey (3rd ed.). Lincoln, RI: QualityMetric Incorporated. 2. Ware et al. 1993
PRO: Patient Reported Outcome, QALY: Quality Adjusted Life Year

Zuranolone Integrated Analyses: Patient Report of Functioning and Well-Being†

- MDD can severely impair patient functioning and well-being[1]
- In an integrated analysis from completed placebo-controlled trials across the LANDSCAPE and NEST programs, patients with MDD or PPD treated with zuranolone reported rapid and sustained improvements in health-related quality of life over time compared to placebo, as measured using SF-36 scores, a patient-reported measure of functioning and well-being†
- These data suggest the potential of zuranolone in improving functioning and well-being measures important to patients with depression
- A recent analysis published in peer reviewed journal PLOS ONE suggested that ADTs did not continue to improve patient's QoL over time[2]



1. Bromet EJ, et al. Cambridge University Press. 2018:41-56. 2. Almohammed A, et al. *PLoS ONE*. 2022;17(4):e0265928. *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. CFB = change from baseline; MMRM = mixed-effect model for repeated measures; SF-36v2 = 36-Item Short Form Health Survey (version 2).

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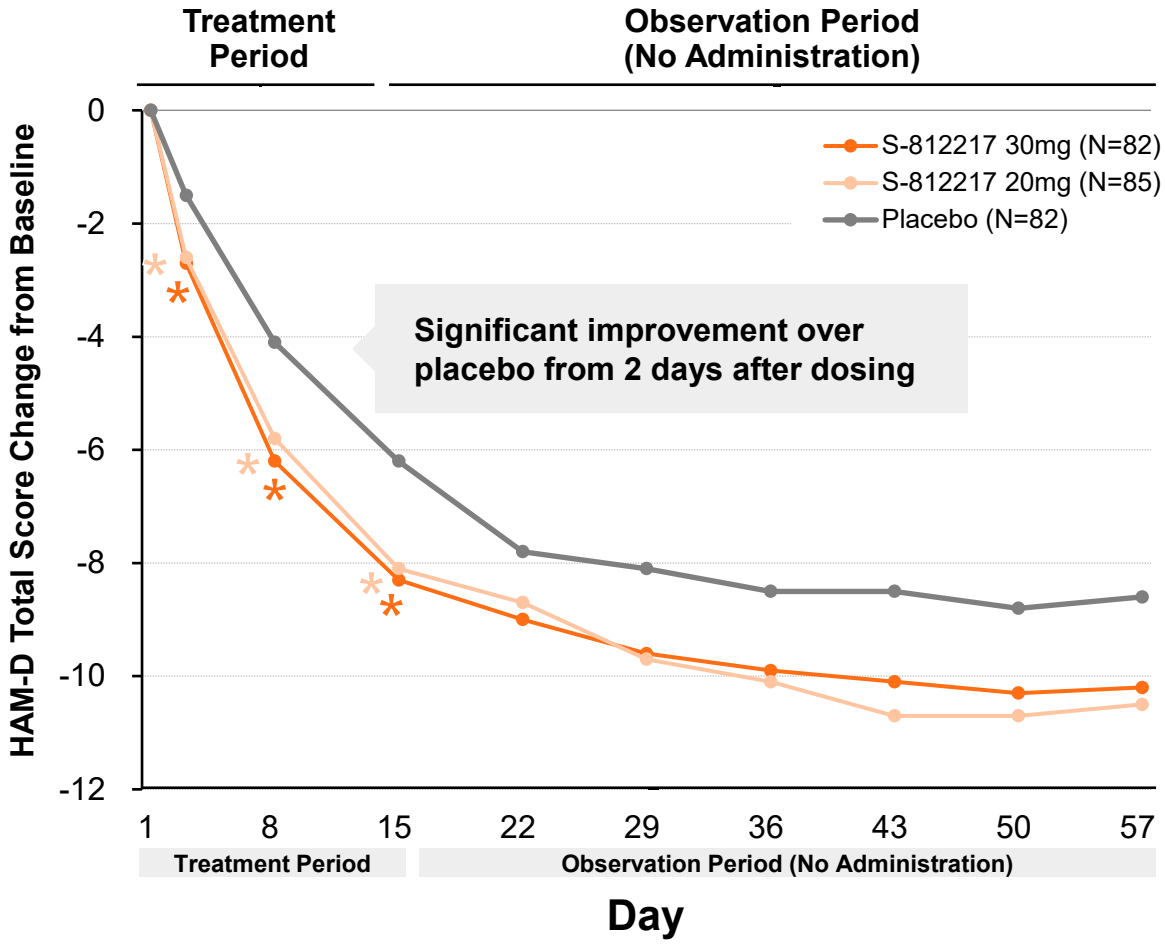
Shionogi Phase 2 Study conducted in Japan shows consistent profile of zuranolone



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

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* P<0.05 vs Placebo. ** Percentage of patients who improved ≥50% in HAM-total score from baseline
Slide presented at the Shionogi R&D Day held on September 29, 2021

General Safety and Tolerability in Placebo-controlled Trials

Safety and Tolerability of Zuranolone Were Generally Consistent Across ROBIN, SKYLARK, MDD-201B, MOUNTAIN, and WATERFALL Studies[1-5]

"The AEs frequently associated with current antidepressant therapies such as weight gain, sexual dysfunction, euphoria and sleep disruption have not been seen to date with zuranolone. These are the adverse effects I have to deal with to help my patients be able to continue to take their standard of care antidepressants and they affect a significant percentage of patients. These symptoms also are typically the cause of treatment discontinuation with standard of care antidepressant drugs."

Anita Clayton, M.D., Chair of Psychiatry and Neurobehavioral Sciences, University of Virginia School of Medicine

Range of TEAEs Across Phase 2 and 3 Placebo-controlled Trials[1,2,*]
ROBIN, SKYLARK, MDD-201B, MOUNTAIN, and WATERFALL Studies

Severity of TEAEs, % (overall range)	Zuranolone 30 mg or 50 mg†
Mild to moderate	94–100
Severe	0–4
Serious	0–2
Most Common (>10%) TEAEs, % (overall range)	**Zuranolone 30 mg or 50 mg†**
Headache	6–18
Somnolence	7–27
Dizziness	5–14
Nausea	3–11
Sedation	4–11

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

- A 14-day treatment course with zuranolone 30 mg or 50 mg was generally well-tolerated in patients with MDD or PPD.[1,2]
- Most AEs associated with zuranolone were mild to moderate in severity.[1,2]
- Most AEs associated with zuranolone occurred during the 14-day treatment course.

***Most common defined as >10% of patients in either zuranolone 30 mg or 50 mg. †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**

AE = adverse event; MDD = major depressive disorder; TEAE = treatment-emergent adverse event; ZRN, zuranolone.

1. Deligiannidis KM, et al. Poster presented at: American Society of Clinical Psychopharmacology Annual Meeting; 31 May-3 Jun 2022; Scottsdale, AZ. 2. Data on file. SAGE-217-PPD-301 Topline results memo, Version 1.0. 25 May 2022. Zuranolone is being developed in collaboration with Biogen.

CORAL Study: Safety/Tolerability through Day 42

- Over the study period, TEAEs ≥10% in either treatment group (zuranolone 50 mg co-initiated with an ADT vs placebo co-initiated with an ADT) were somnolence, dizziness, headache, and nausea.[1,2]
- The percentage of people reporting TEAEs leading to discontinuation of study drug were 6.6% in the zuranolone co-initiated with an ADT arm, and 3.7% in the ADT co-initiated placebo arm, respectively. Similarly, the percentage of people reporting TEAEs leading to discontinuation of ADT were 7.5% in the zuranolone co-initiated with an ADT arm, and 5.5% in the ADT co-initiated with placebo arm, respectively.
- No safety signal of increased suicidal ideation/behavior was noted with zuranolone 50 mg when co-initiated with an ADT compared to placebo co-initiated with an ADT.[1,2*]
- No evidence of withdrawal symptoms was observed after discontinuation of zuranolone 50 mg co-initiated with an ADT following the treatment period.[1,2†]

TEAEs Incidence (≥10% in either treatment group) through Day 42[1]

	Placebo co-initiated with an ADT N = 218‡ n (%)	Zuranolone 50 mg co-initiated with an ADT N = 212‡ n (%)
Somnolence	18 (8.3)	39 (18.4)
Dizziness	16 (7.3)	28 (13.2)
Headache	32 (14.7)	25 (11.8)
Nausea	51 (23.4)	19 (9.0)

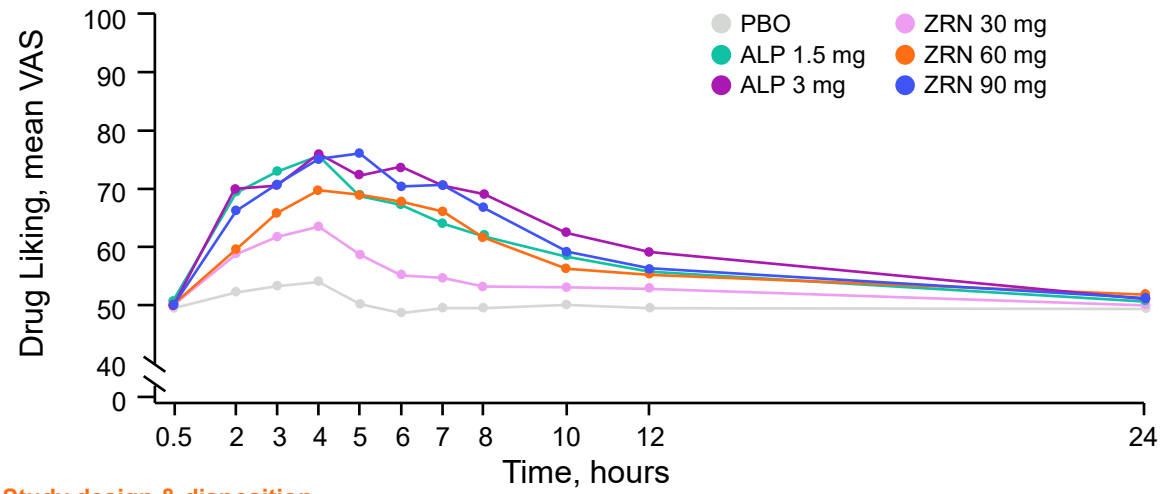
*Suicidality was assessed with the C-SSRS. †Withdrawal symptoms were assessed with the PWC-20 at Days 18 or 21. Scores were similar after discontinuation of zuranolone 50 mg or placebo. ‡N value is based on the safety set, which is defined as all patients administered blinded zuranolone 50 mg or placebo.
ADT = antidepressant therapy; TEAE = treatment-emergent adverse event.

1. Parikh, SV. et al. Presented at American Society of Clinical Psychopharmacology Annual Meeting; May 31 – June 3, 2022

Zuranolone is being developed in collaboration with Biogen.

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

Mean VAS scores for Drug Liking Over Time[7]



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 phase[7]
- Treatment phase: Randomized, double-blind active and PBO-controlled, 6-way crossover design; N=60 completed treatment phase[7]

- **Zuranolone 30 mg and 60 mg demonstrated lower abuse potential compared with alprazolam 1.5 mg and 3mg[7]**
- **Zuranolone 90mg was comparable to alprazolam[7]**

- 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 alprazolam[7]
- 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, Neuropharamcology; 2020. 2. Martinez Botella G, et al. Med Chem. 2017. 3. Schwienteck 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.

Sage Therapeutics®

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

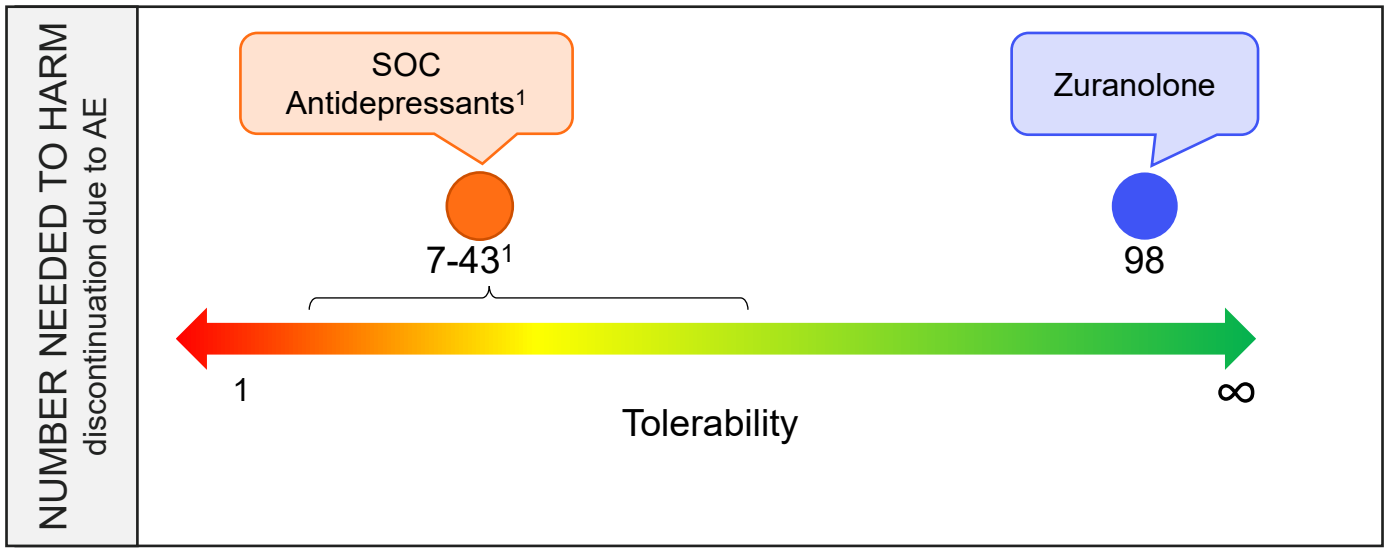
Discontinuation due to AEs is commonly utilized in MDD for NNH calculations

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.

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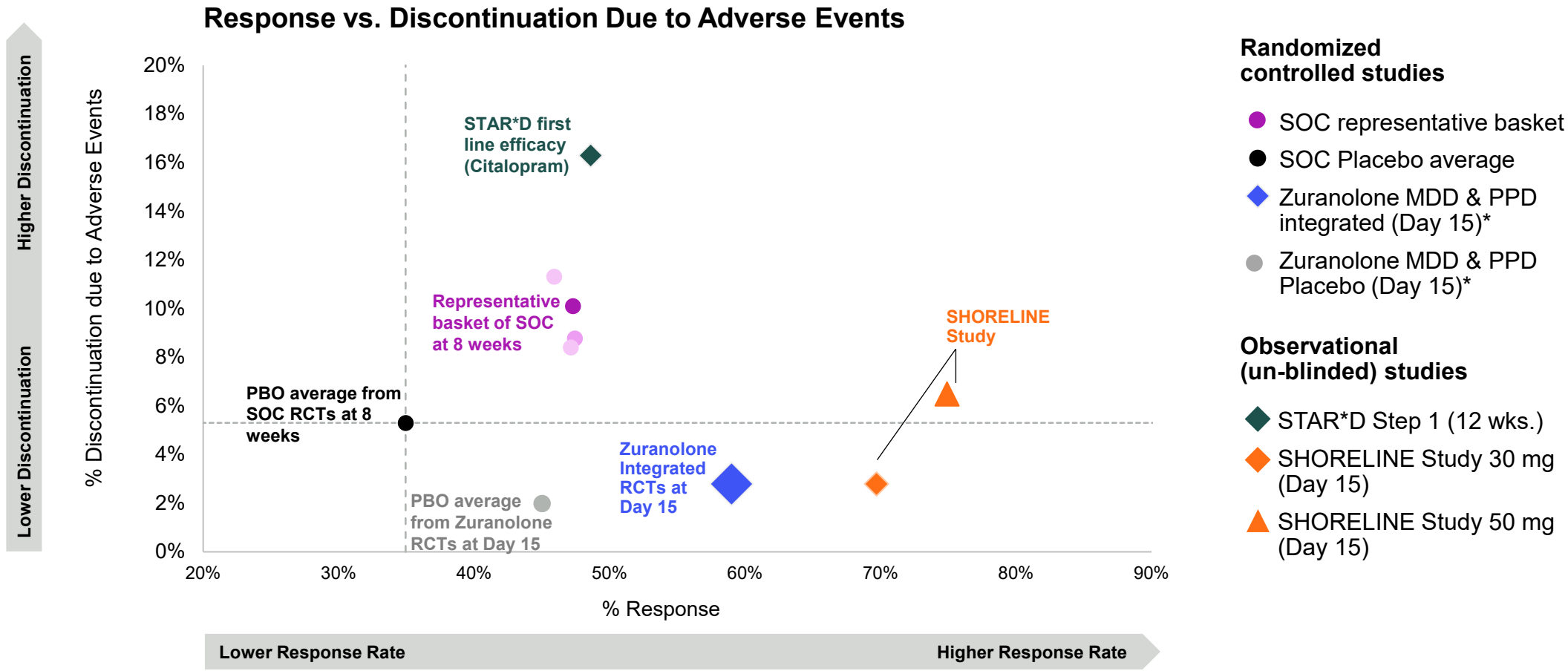
Integrated analyses include ROBIN Study, MDD-201B Study, MOUNTAIN Study (≥24 HAMD-17 subgroup), and WATERFALL Study. 1.Citrome 2016 *J Affective Disorders*

*Includes data from MDD-201B, MOUNTAIN, WATERFALL and ROBIN Studies; data from CORAL Study are not included

Zuranolone is being developed in collaboration with Biogen.

GABA PAM

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



Randomized controlled studies

- SOC representative basket
- SOC Placebo average
- Zuranolone MDD & PPD integrated (Day 15)*
- Zuranolone MDD & PPD Placebo (Day 15)*

Observational (un-blinded) studies

- STAR*D Step 1 (12 wks.)
- SHORELINE Study 30 mg (Day 15)
- SHORELINE Study 50 mg (Day 15)

- Methods: Average response (>50% reduction from baseline) and discontinuation due to side effects rates for SOC were obtained from Cipriani et al. 2018 (average placebo for SOC trials and representative basket of SOC products), and for zuranolone from an integrated analysis of zuranolone clinical data; SHORELINE Study and STAR*D, which was included for real-world context.
- 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 above.

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*Integrated analyses combine doses from ROBIN Study, MDD-201B Study, MOUNTAIN Study (≥24 HAMD-17 subgroup), and WATERFALL Study.

Zuranolone is being developed in collaboration with Biogen.

Sage's planned commercialization 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 low/no access hurdles	**Mobilize** targeted HCPs to identify and treat zuranolone patient types in MDD and PPD
Payors	Efficacious, cost-effective solution for MDD and PPD patient types associated with poorer outcomes	**Connect** treatment outcomes in MDD and PPD with zuranolone performance through innovative proactive Value Based Agreements to drive at-launch access
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

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Zuranolone is being developed in collaboration with Biogen.

Potential clinical use scenarios for zuranolone in MDD

Across these different clinical scenarios, *MDD with elevated anxiety is a common presentation*

"Major depressive disorder with elevated anxiety is a common presentation of depression and is associated with a more prolonged and severe disease course and poor response to current treatments. Data from the LANDSCAPE and NEST clinical development programs suggest that, if approved, zuranolone may offer the potential for patients with MDD and PPD with or without elevated anxiety to experience rapid improvements."

Maurizio Fava, M.D.
Psychiatrist-In-Chief, Vice Chair, the Massachusetts General Hospital (MGH) Executive Committee on Research
Executive Director, Clinical Trials Network and Institute, MGH
Associate Dean for Clinical and Translational Research, Slater Family Professor of Psychiatry, Harvard Medical School

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Zuranolone is being developed in collaboration with Biogen.

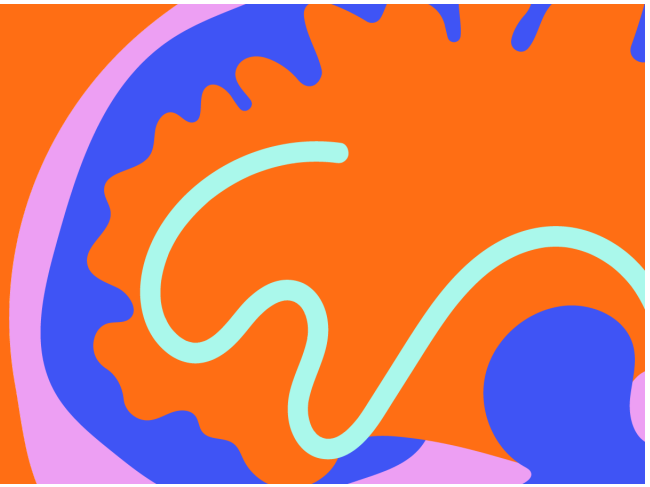
Neuropsychiatry Franchise

Neuropsychiatric disorders

Preserving independence through the treatment of cognitive impairment

- Globally, disorders involving cognitive dysfunction continue to increase
- These disorders represent one of the greatest areas of unmet need
- Significant impact on patients' ability to work, live independently, adhere to medical care, and interact with family
- Sage is forging new pathways

Global Prevalence



~188K	~8.8M	~134M
Huntington's Disease	Parkinson's Disease	Alzheimer's Disease

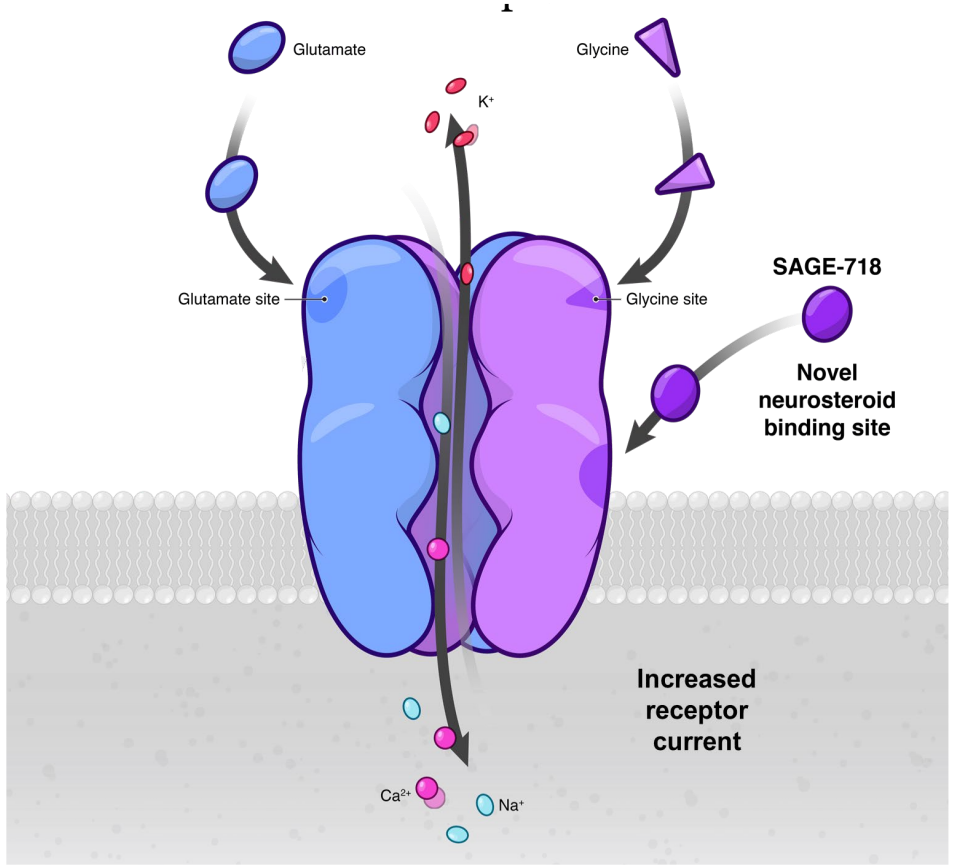
Sage Therapeutics

Re-thinking treatment of neuropsychiatric disorders

Sage has developed a robust library of NMDA receptor modulators

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

Endogenous & Exogenous Ligands at the NMDA Receptor



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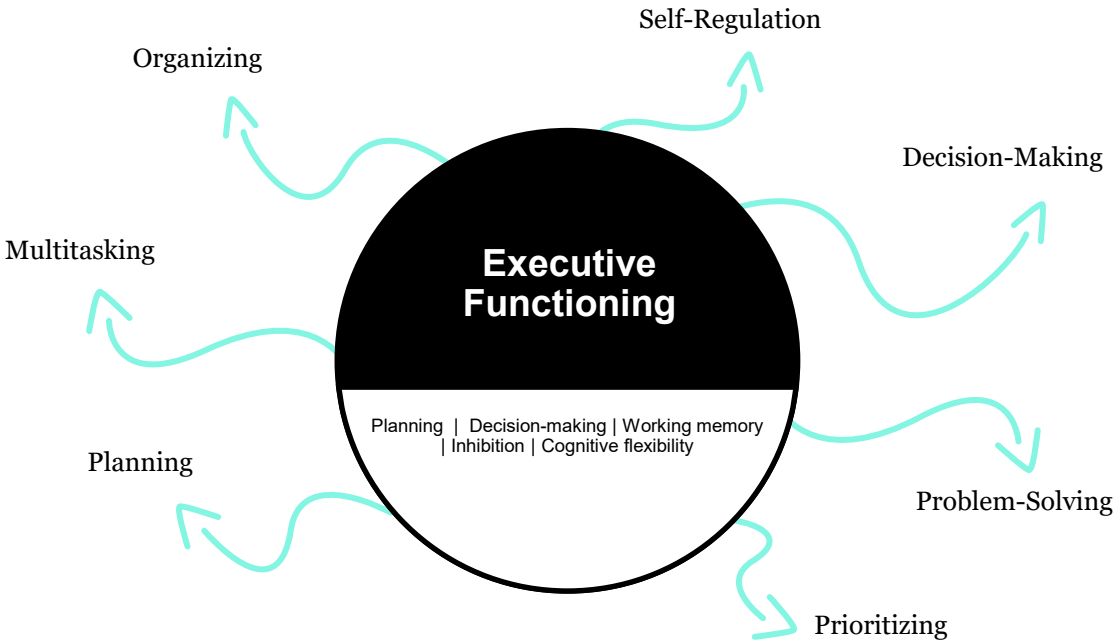
SAGE-718: Goal of improving cognitive and executive function

Potential to provide unique cognitive benefits for patients with neurodegenerative disorders

- SAGE-718 profile well-suited for study of potential to benefit executive function in patients with neurodegenerative disorders:
  - Clinical findings from Phase 1 studies suggest potential to improve executive function, a key component of brain health across life-span
- Ongoing exploration in areas of cognitive dysfunction in diseases with high unmet need, including Alzheimer's, Parkinson's, and Huntington's diseases
- Five Phase 1 studies to date and two Phase 2 open-label studies – generally well-tolerated and with meaningful activity suggesting potential in brain health disorders



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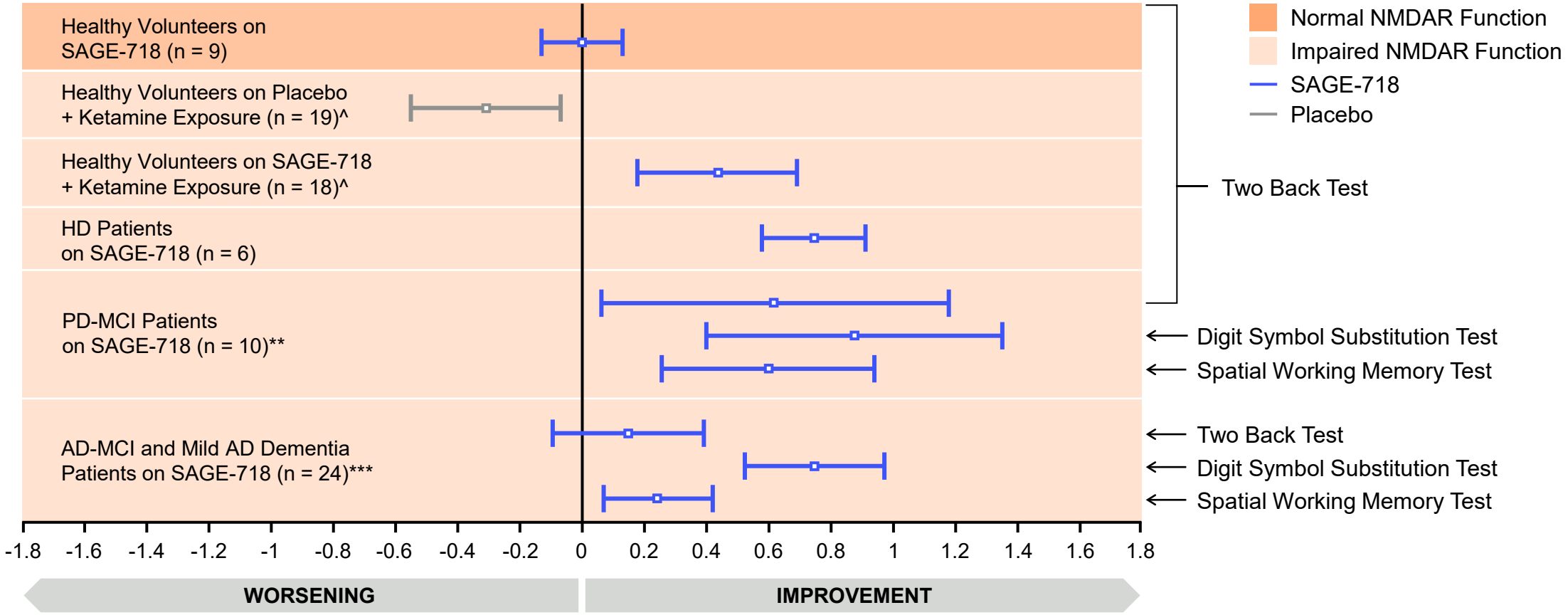
SAGE-718 demonstrated improvements in cognitive function in early clinical trials

Performance on Executive Tasks in Healthy Volunteers and Patients with Huntington's, Parkinson's, and Alzheimer's Diseases

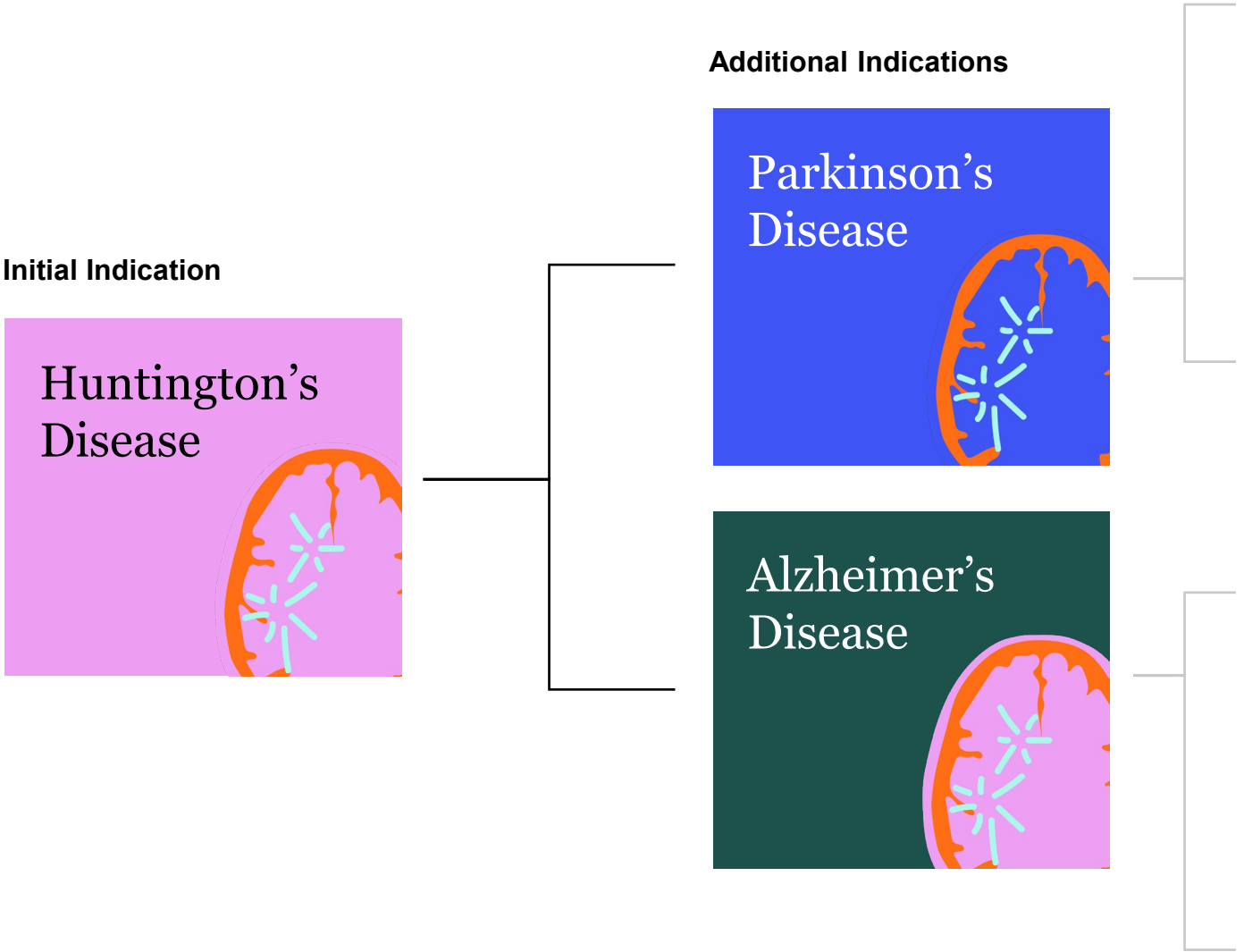
Z-Transformed Change from Baseline to Last Assessment* (Mean ± SE Plotted)



*Last assessment at day 14 for HV study, day 10 for HV ketamine study, day 14 for HD study, day 14 for PD/AD Two Back, and day 28 for PD/AD DSST and SWM
**n=6 for Two Back, n=9 for DDST
***n=21 for Two Back, n=23 for SWM

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 (study ongoing) and Alzheimer's diseases
- Leveraging learnings across indications designed to help de-risk program



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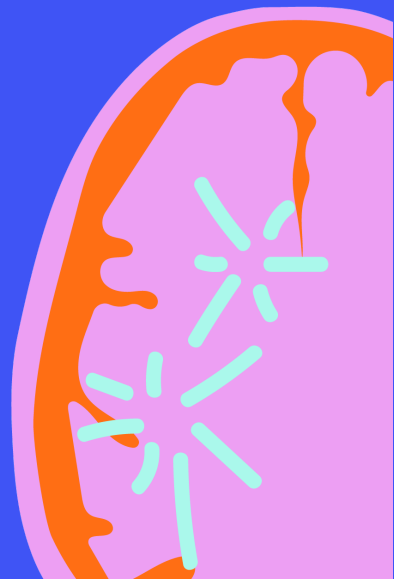
SAGE-718 clinical development program designed to define potential benefits and leverage learnings

Huntington's Disease & CogNEXT Clinical Signal-Finding Studies



Phase 1

CLP-102-B
Completed
Open-label study in HD

Phase 2

DIMENSION (CIH-201)
Enrolling
Randomized study in HD

PARADIGM (CNP-201)
Complete
Open-label study in PD

LUMINARY (CNA-201)
Complete
Open-label study in AD

SURVEYOR (CIH-202)
Enrolling
Randomized Study in HD

PRECEDENT (CNP-202)
Enrolling
Randomized Study in PD

LIGHTWAVE (CNA-202)
Planned Late 2022 (Start)
Randomized Study in AD

Phase 3

CIH-301
Planned Late 2022 (Start)
Safety study in HD

- Huntington's
- Parkinson's
- Alzheimer's
- FDA Fast-track Designation

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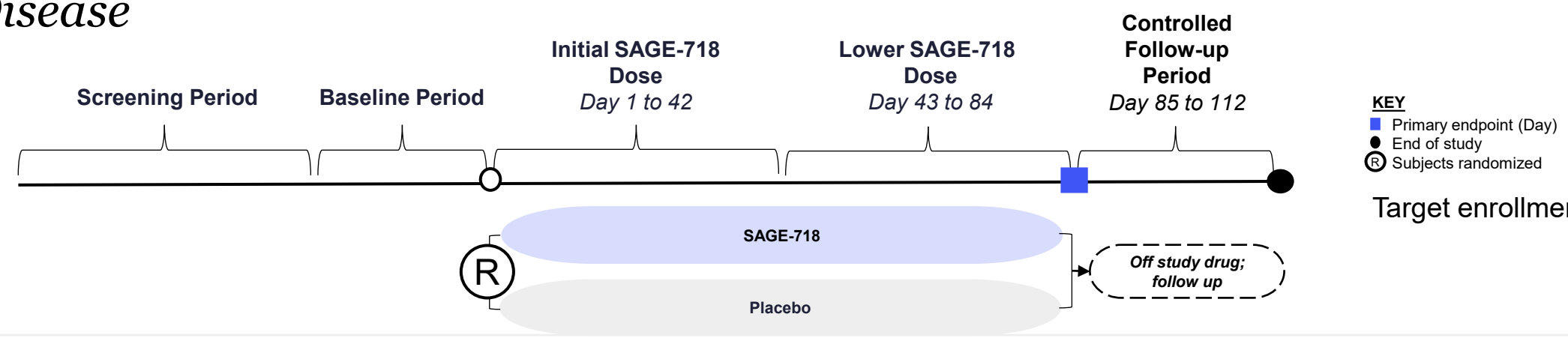
Abbreviations: HD = Huntington's Disease, PD = Parkinson's Disease, AD = Alzheimer's Disease, PBO = Placebo, PK = Pharmacokinetics, MRI = Magnetic Resonance Imaging

LIGHTWAVE Study - SAGE-718

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



Target enrollment = 150

STUDY OVERVIEW

Status	Start-up
Indication	MCI or Mild Dementia due to Alzheimer's disease
Phase	Phase 2
Arms	Double-blind, randomized: 1:1 • SAGE-718, placebo
Dosing Regimen	Initial Dose (Days 1 to 42), then Lower dose (Days 43 to 84)

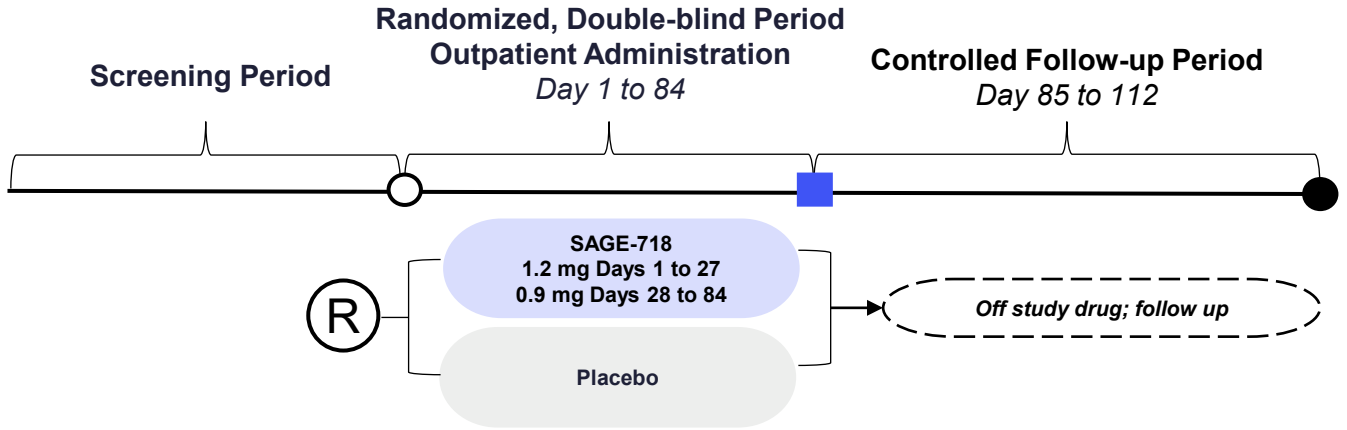
Objectives	• To evaluate the effect of SAGE-718 on cognitive performance in participants with Mild Cognitive Impairment (MCI) or mild dementia due to Alzheimer's (AD) • To evaluate the safety and tolerability of SAGE-718 oral capsule in participants with MCI or mild dementia due to AD
Primary Endpoint	• Change from Baseline to Day 84 in the Wechsler Adult Intelligence Scale-IV (WAIS-IV) Coding test
Key Secondary Endpoint	• 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)

Inclusion Criteria	• Be between the ages of 50 and 80 at Screening
	• Meet all the following criteria for MCI or mild dementia due to AD:
	  • 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

Exclusion Criteria	• 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



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

Target enrollment = 178

STUDY OVERVIEW

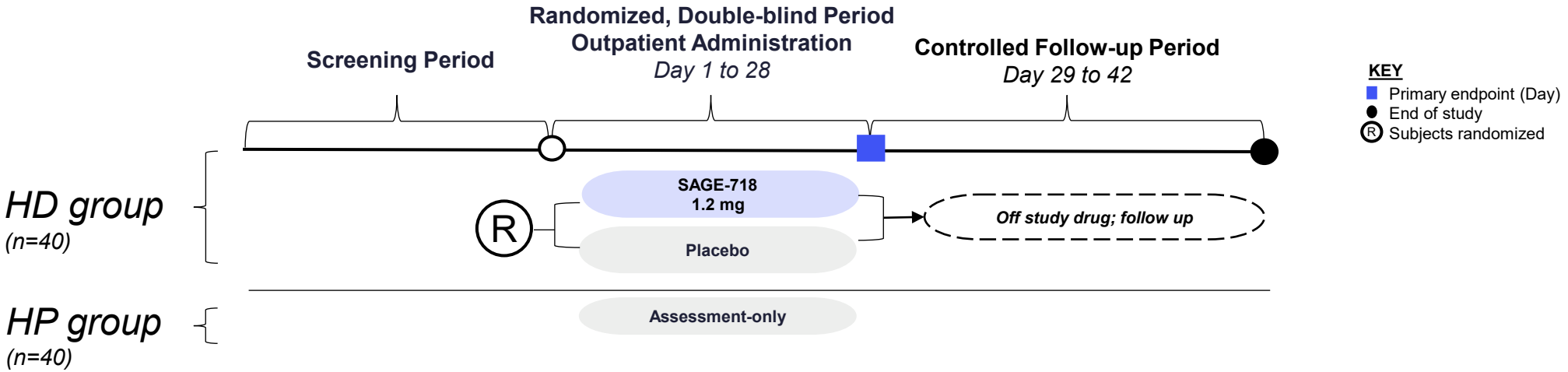
Status	Enrolling	**Primary Endpoint**	• Change from baseline in Composite score of the Huntington's Disease Cognitive Assessment Battery (HD-CAB)
Indication	Huntington's disease Cognitive Impairment	**Key Secondary Endpoint**	• UHDRS Independence Scale

Phase	Phase 2	**Inclusion Criteria**	• Be at least 25 years old but no older than 65 years of age at Screening
			• Meet all the following criteria for HD:
			  • 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 • SAGE-718, placebo		
Dosing Regimen	1.2 mg oral daily from days 1 to 27; 0.9 mg oral daily from days 28 to 84	**Exclusion Criteria**	• 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

SURVEYOR Study - SAGE-718

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



STUDY OVERVIEW

Status	Enrolling
Indication	Huntington's disease Cognitive Impairment
Phase	Phase 2
Arms	Double-blind, randomized: 1:1 (HD) • SAGE-718, placebo Assessment-only comparator arm (HP)
Dosing Regimen	1.2 mg oral daily

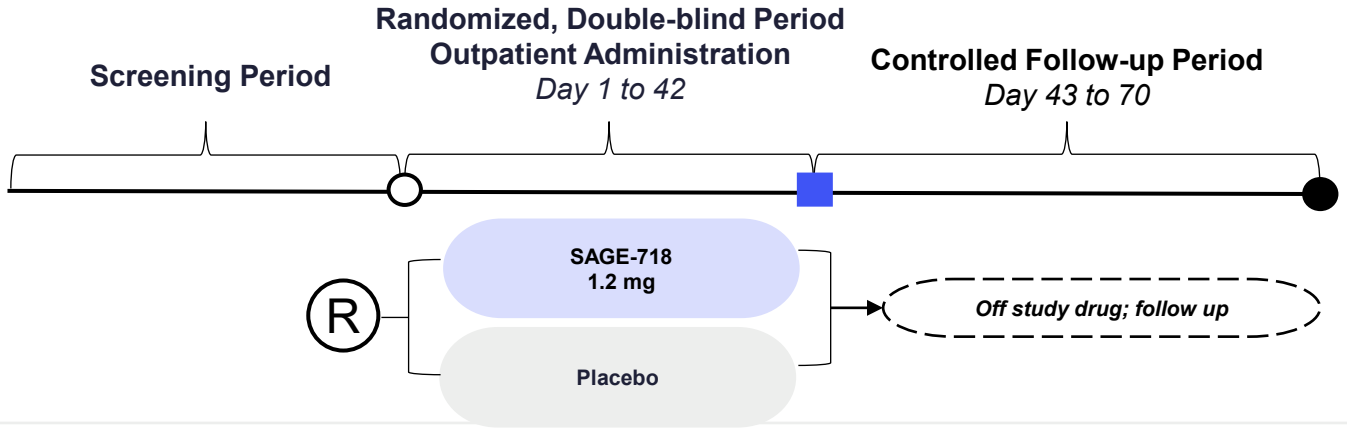
Objectives	• To assess the magnitude of the baseline difference between participants with early Huntington's Disease (HD) and healthy participants (HP) with respect to measures of cognitive performance. • To evaluate the effect of SAGE-718 on cognition and functioning outcomes in participants with HD
Primary Endpoint	• Baseline measures of the Huntington's disease Cognitive Assessment Battery (HD-CAB) cognitive composite score.
Secondary Endpoints	• Change from Baseline to Day 28 on HD-CAB, VRFCAT, other endpoints. • Safety and tolerability of SAGE-718

Inclusion Criteria (HD Participants)	• Be at least 25 years old but no older than 65 years of age at Screening
	• Meet all the following criteria for HD:
	  • 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

Exclusion Criteria (HD Participants)	• 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



KEY
- Primary endpoint (Day)
- End of study
- Subjects randomized

Target enrollment = 76

STUDY OVERVIEW

Status	Enrolling
Indication	Mild Cognitive Impairment (MCI) due to Parkinson's disease
Phase	Phase 2
Arms	Double-blind, randomized: 1:1 • SAGE-718, placebo
Dosing Regimen	1.2 mg oral daily
Objectives	• 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
Primary Endpoint	• Change from Baseline to Day 42 in the Wechsler Adult Intelligence Scale-IV (WAIS-IV) Coding test
Key Secondary Endpoint	• Proportion of participants experiencing treatment emergent adverse events (TEAEs) and severity of TEAEs. • Number of participants who withdraw due to adverse events (AEs).

Inclusion Criteria	• Be between the ages of 50 and 75 at Screening
	• Meet all the following criteria for PD-MCI:
	  • 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

Exclusion Criteria	• 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 Franchise

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 Therapeutics®

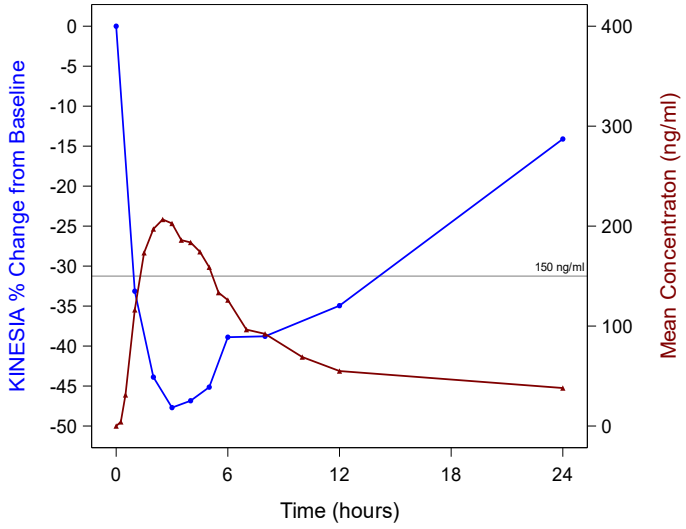
Sources: 1) Data from HEOR survey of 108 US ET-treating physicians, 1,003 patient records, 476 patient reports, and 253 caregiver reports

SAGE-324: Novel potential treatment for movement disorders

Predictable PD effects and PK profile with long half-life

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

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



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

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

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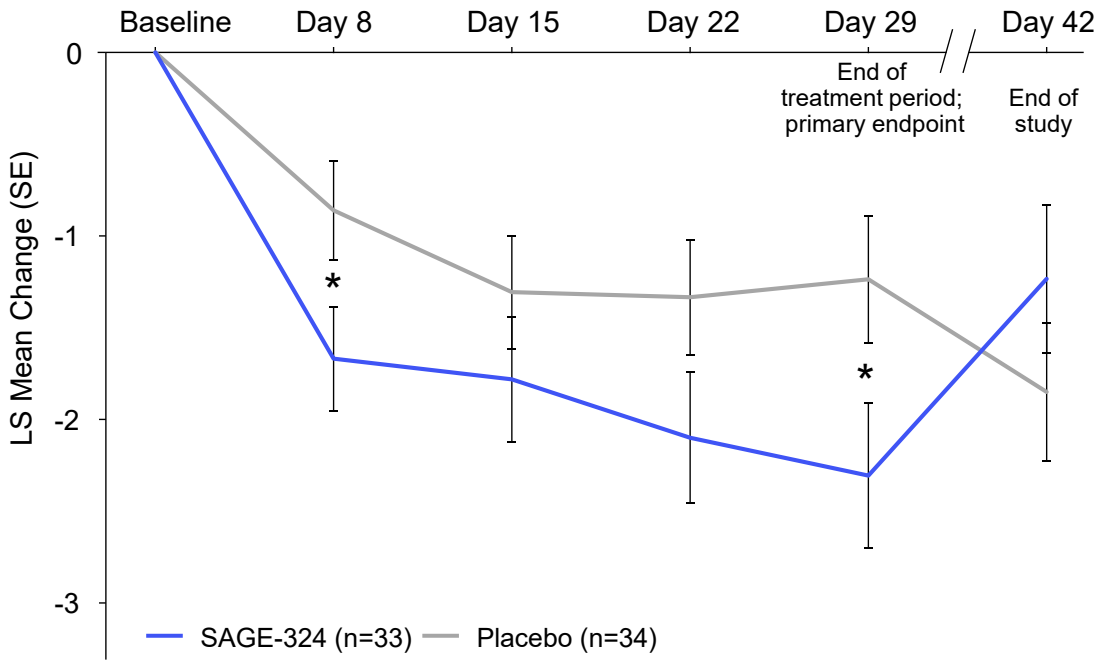
SAGE-324 is being developed in collaboration with Biogen.

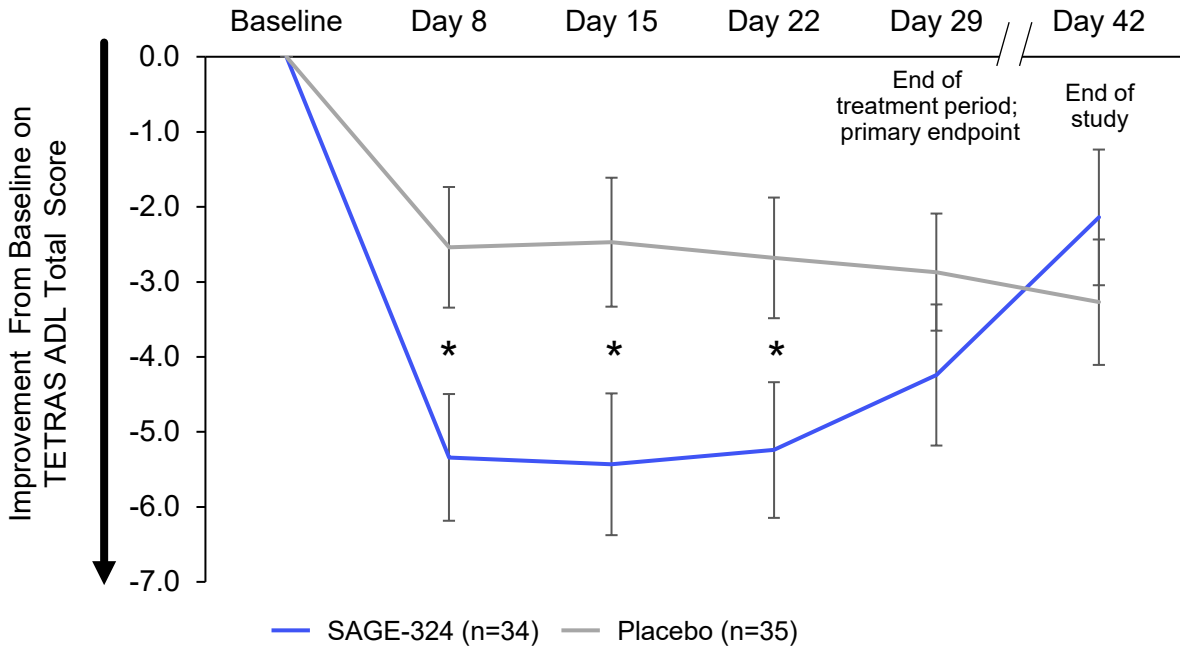
Improvement in tremor control and ADL score observed in the KINETIC Study

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



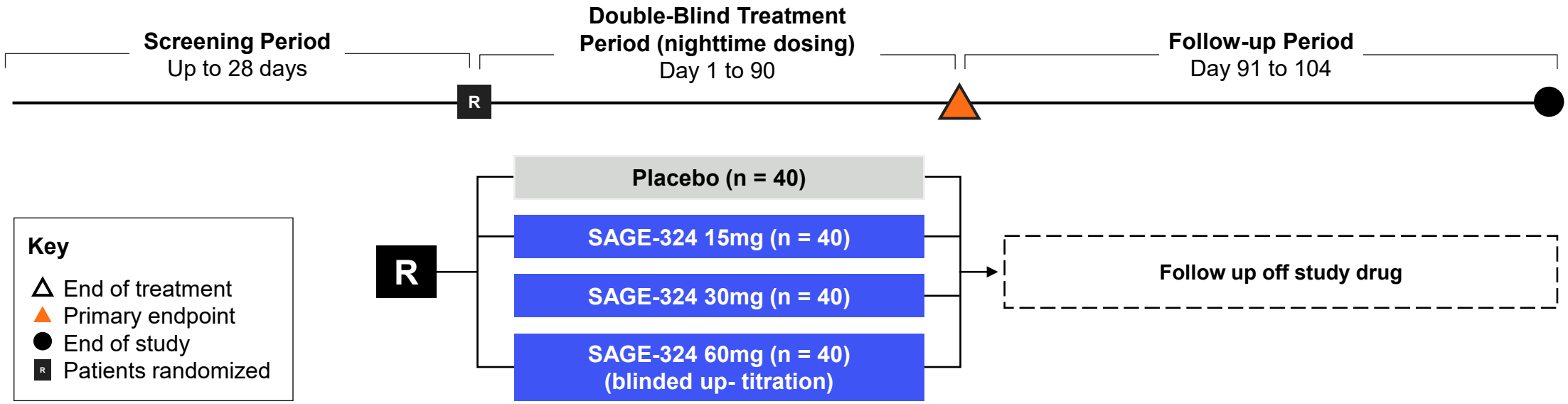
Baseline mean (SD) TETRAS ADL Subscale Total Score: placebo 26.7 (6.84); SAGE-324 26.3 (8.50)

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%).

*p<0.05 (Secondary/other endpoints were not adjusted for multiplicity; p-values are nominal)
Sage Therapeutics, Inc. Data on file.

SAGE-324 is being developed in collaboration with Biogen.

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

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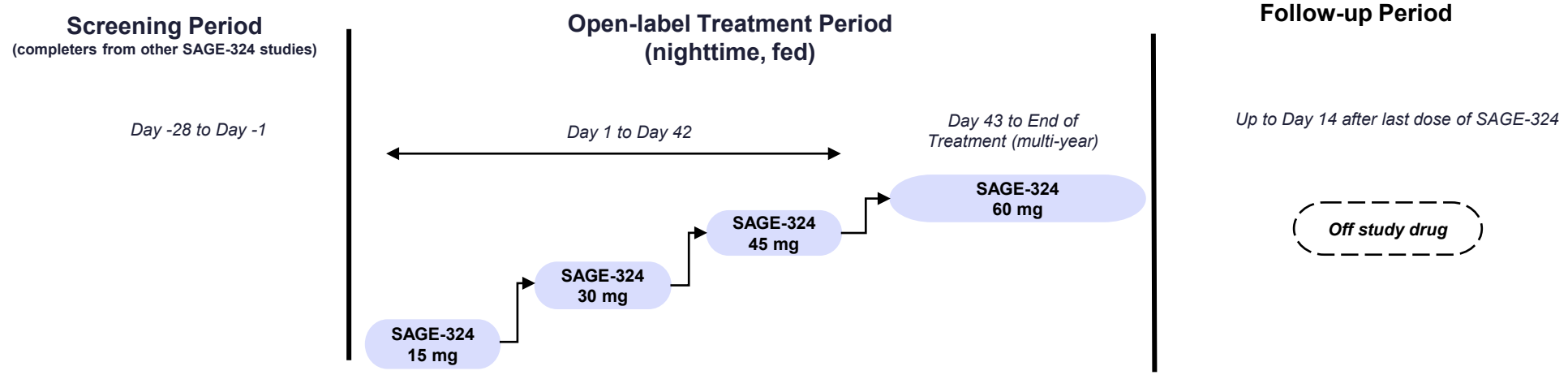
SAGE-324 is being developed in collaboration with Biogen.

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

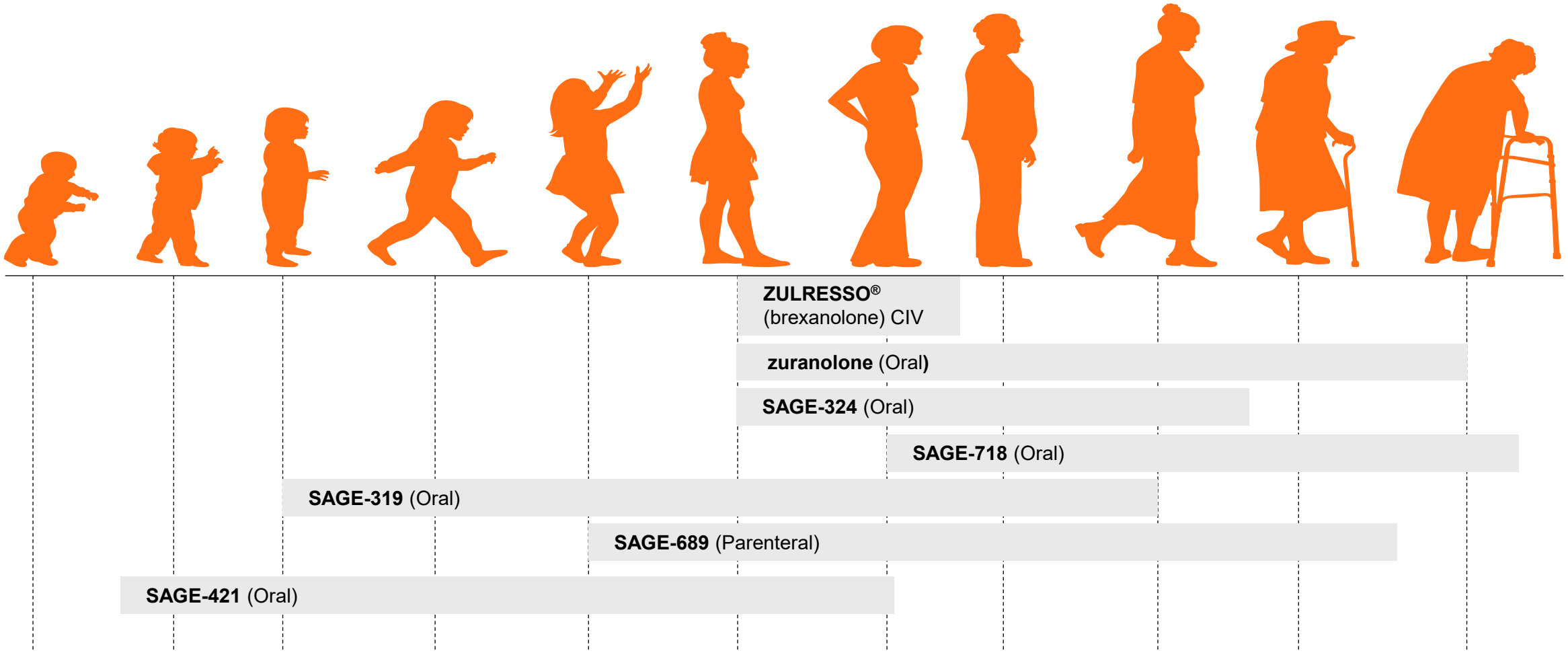
Status	Initiated
Indication	Essential Tremor
Phase	Phase 2
Arms	Open-label • SAGE-324
Dosing Regimen	Up titration in 15mg increments to 60mg Nighttime, fed

Objectives	• To assess the long-term safety and tolerability of SAGE-324
Primary Endpoint	• Incidence of treatment-emergent adverse events (TEAEs)
Key Secondary Endpoint	• 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
Inclusion Criteria	• 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: a. Duration of at least 3 years b. 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 c. Absence of historical or clinical evidence of tremor with psychogenic origin • Participant has successfully completed participation in another SAGE-324 study
Exclusion Criteria	• 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-324 is being developed in collaboration with Biogen.

Sage proprietary product engine

Sage's robust portfolio features NCEs with differentiated target profiles that are 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

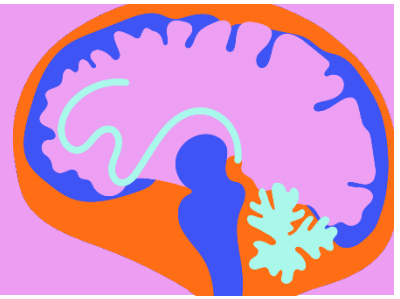
Continuing Innovation with the GABA and NMDA platforms

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

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Third Quarter 2022 Financial Results

Strong financial position with $1.4B in cash

Item	Q3 ‘22	Q3 ’21
Revenue	*$1.7M*	*$1.4M*
R&D Expense	$81.6M	$83.5M
SG&A Expense	$61.5M	$48.7M
Cost of Goods Sold	$0.2M	$0.1M
Total Operating Costs and Expenses	$143.2M	$132.3M
Net Loss	($137.3M)	($130.2M)
Cash and Marketable Securities	$1.4B	$1.8B

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Anticipated 2022 Milestones

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

	Early	Mid	Late	
DEPRESSION FRANCHISE				
Zuranolone (SAGE-217)	✓			Report topline data from CORAL Study in MDD
	✓			Initiate rolling submission of NDA filing package for the treatment of MDD and PPD
		✓		Report topline data from SKYLARK Study in PPD
			●	Complete rolling submission of NDA filing package for the treatment of MDD (December 2022)
	✓	✓	✓	Present additional analyses of data from LANDSCAPE and NEST clinical programs, including health economics and patient reported outcomes
NEUROLOGY FRANCHISE				
SAGE-324		✓		Initiate Phase 2 safety study
	✓	✓	✓	Present additional analyses of data from clinical development program
NEUROPSYCHIATRY				
SAGE-718		✓		Initiate placebo-controlled Phase 2 Study in Parkinson's disease
		✓		Initiate SURVEYOR Study in Huntington's disease
			●	Initiate Huntington's disease open label extension study
			●	Initiate placebo-controlled Phase 2 Study in Alzheimer's disease cognitive impairment
	✓	✓	✓	Present additional analyses of data from clinical development program
ADDITIONAL CLINICAL PROGRAMS				
Additional Pipeline Programs		●		Present data on early-phase studies for pipeline programs
			●	Provide update on next steps for pipeline programs

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 2022 and beyond

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

Expect to progress six Phase 2 studies in 2022 and submit NDA filing seeking approval for second marketed product

Focused on plans for potential commercialization for later-stage programs

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

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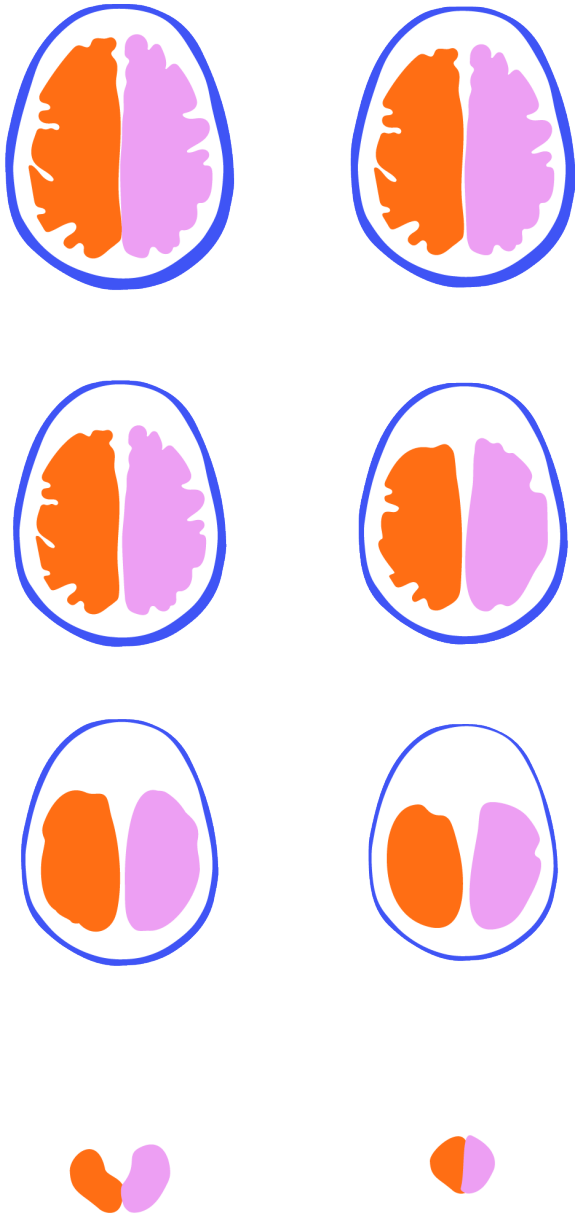
Appendix

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

Sage Therapeutics

Strategic Zuranolone Collaboration with Shionogi

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

Sage Therapeutics™ + SHIONOGI

$90M

Upfront payment

$485M

Potential development & commercial milestones

Strategic Zuranolone and SAGE-324 Collaboration with Biogen

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

Sage Therapeutics™ + Biogen®

$1.5B

Upfront payment and equity investment

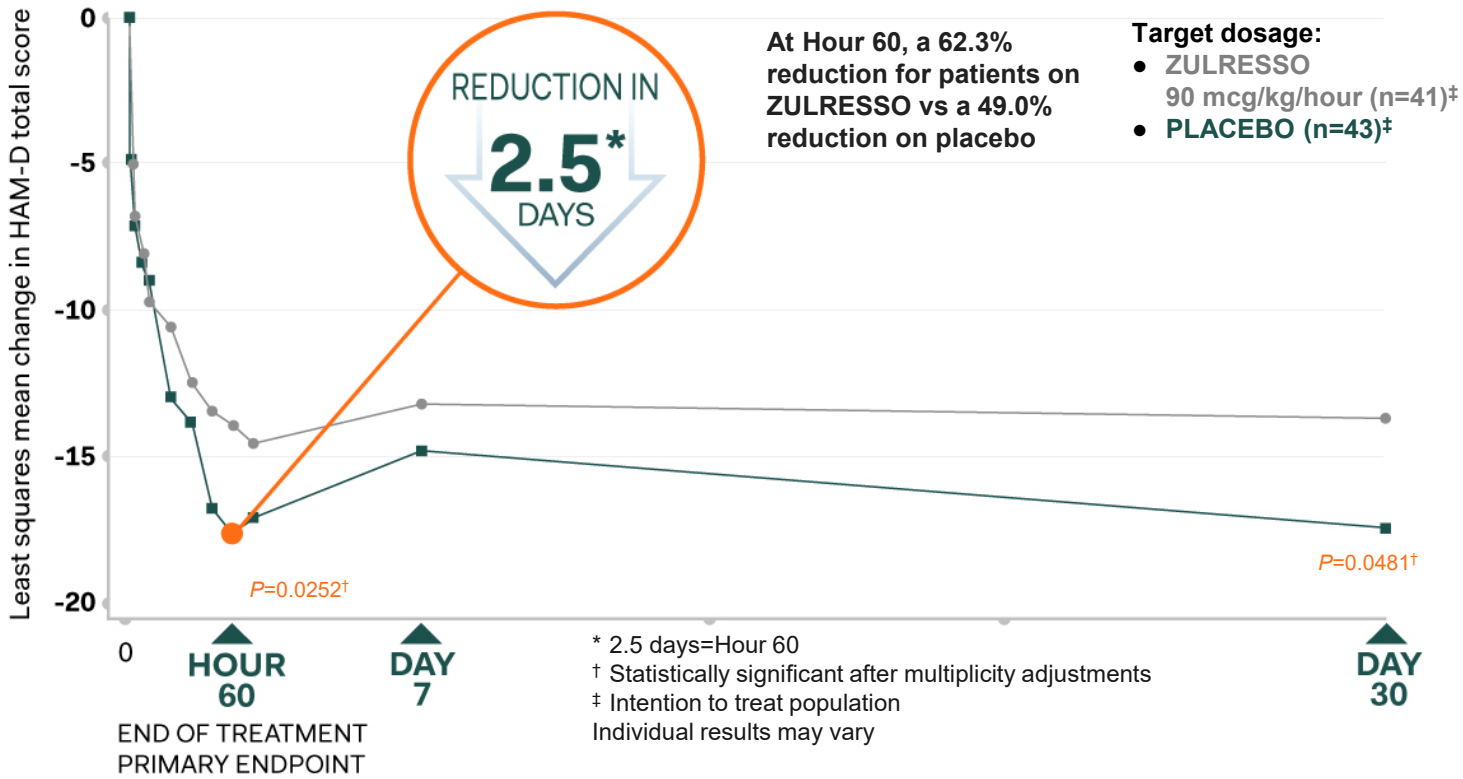
$1.6B

Potential development & commercial milestones

ZULRESSO® (brexanolone) CIV Injection

Treated patients experienced rapid improvement of depressive symptoms

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



Durable therapeutic effect

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

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

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

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

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

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

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

Sage Therapeutics

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

ZULRESSO® (brexanolone) CIV Injection

Boxed warning

WARNING: EXCESSIVE SEDATION AND SUDDEN LOSS OF CONSCIOUSNESS

See full prescribing information for complete boxed warning.

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

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ZULRESSO® (brexanolone) CIV injection

Select Important Safety Information

These are not all the side effects of ZULRESSO.

ZULRESSO can cause serious side effects, including:

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

ZULRESSO can cause other serious side effects, including:

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

The most common side effects of ZULRESSO include:

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

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

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

While receiving ZULRESSO, avoid the following:

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

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

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

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

Sage Therapeutics®

Seeing the brain differently *makes a world of difference*

Sage Therapeutics