



Investor Presentation

February 2022



Safe Harbor Statement

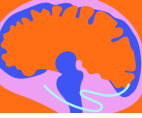
- The slides presented today and the accompanying oral presentations contain forward-looking statements, which may be identified by the use of words such as “may,” “might,” “will,” “should,” “can,” “expect,” “plan,” “anticipate,” “believe,” “estimate,” “project,” “intend,” “future,” “opportunity,” “goal,” “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; our belief that we have sufficient data to file an NDA for zuranolone, the potential regulatory pathways for filing and approval of zuranolone, expected timelines for filings and the potential for approval; 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; the potential for commercialization of zuranolone and anticipated launch timing; our expectations for our commercialization plan; the potential for success of our other product candidates in various indications, including the potential profile and benefit of our other product candidates; our estimates as to the number of patients with disorders and diseases of interest to us and that we hope to help and the potential market for 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 and future funding of operations; and our belief in our ability 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:
 - 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.
 - Continued or extended surges of the COVID-19 pandemic may have a more significant impact on our clinical development timelines, data or business than we expect.
 - 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;
 - The FDA and other regulatory authorities may ultimately decide that the design or results of our completed, ongoing or planned clinical trials for zuranolone or any of our other product candidates, even if positive, are not sufficient to file for or obtain regulatory approval in the indications that are the focus of our development plans despite prior regulatory advice. We may not meet our expected time-lines for filing an NDA for zuranolone or for approval or launch. 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;
 - 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, 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. We may never be successful or achieve our goals with respect to commercialization.
 - 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 our 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
 - 2 or more INDs per year by 2023
 - Launch a new product or indication every 12-24 months starting in 2023
- \$1.7B+ capital/collaborations to fund efforts to accelerate and advance medicines
- Potential to impact an estimated >450M patients globally



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 Organization¹
 - 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 pharmacotherapy²
 - PPD often presents as depression with elevated anxiety³

In a survey of MDD patients conducted by Sage:

68% reported that they were not satisfied with the amount of time they take medication⁴

75% reported being frustrated with the need to switch and try multiple options to treat their MDD⁴



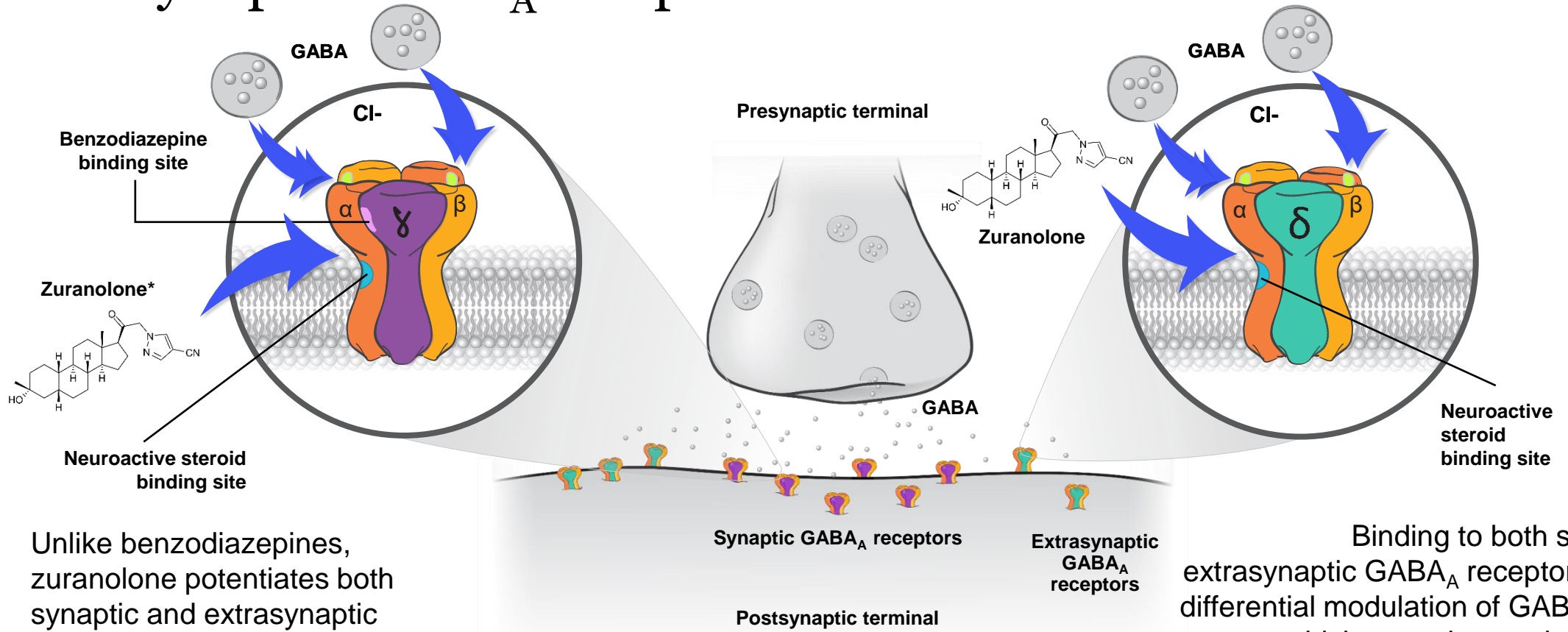
¹Bromet 2018

²Wu 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

³Fairbrother 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

⁴Sage 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 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

*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.

4. Hoffman E et al. *Clin Pharm.* 2020;59(1):111-120.

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

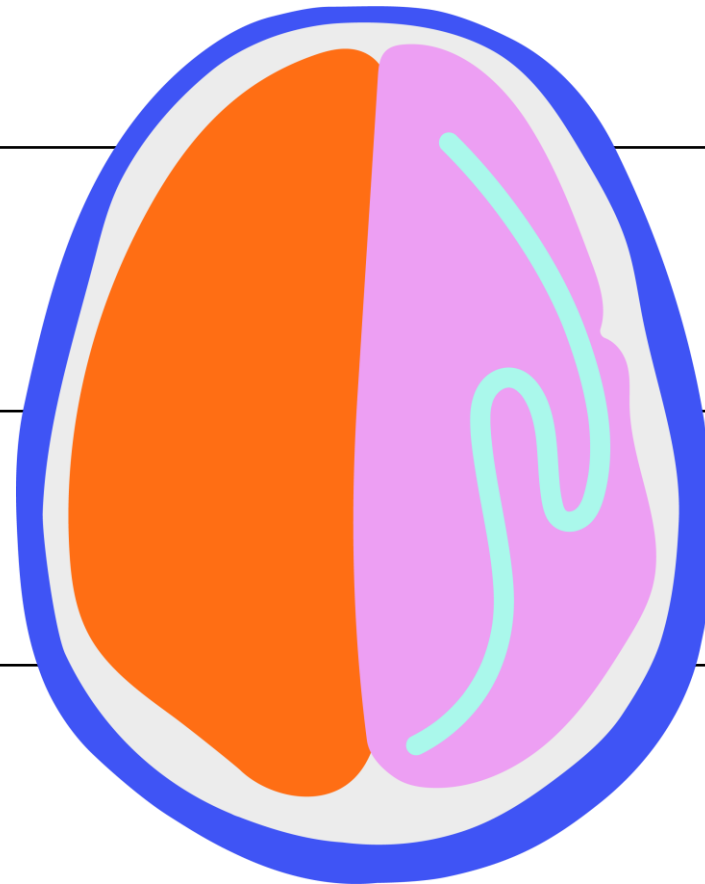
- Rapid response
- Sustained effects lasted beyond completion of treatment

Well-Tolerated

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

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

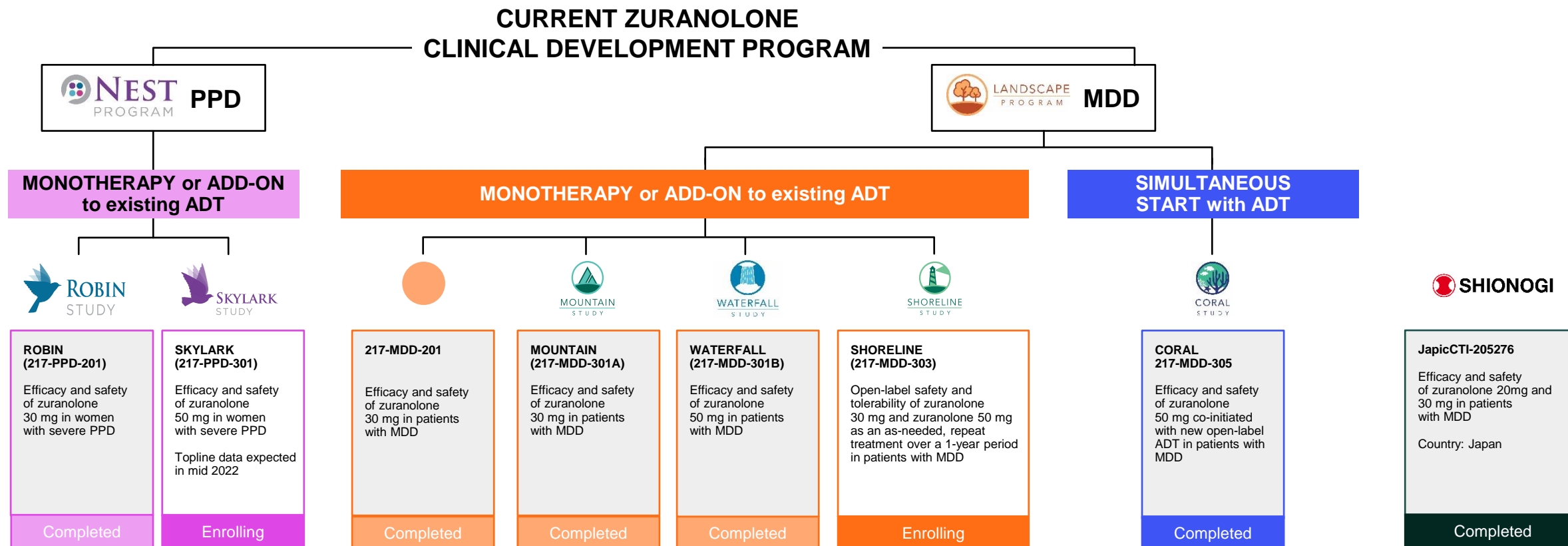
- Selectively modulates GABA_AR
- May help neuronal networks rebalance¹

Flexible Approach

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

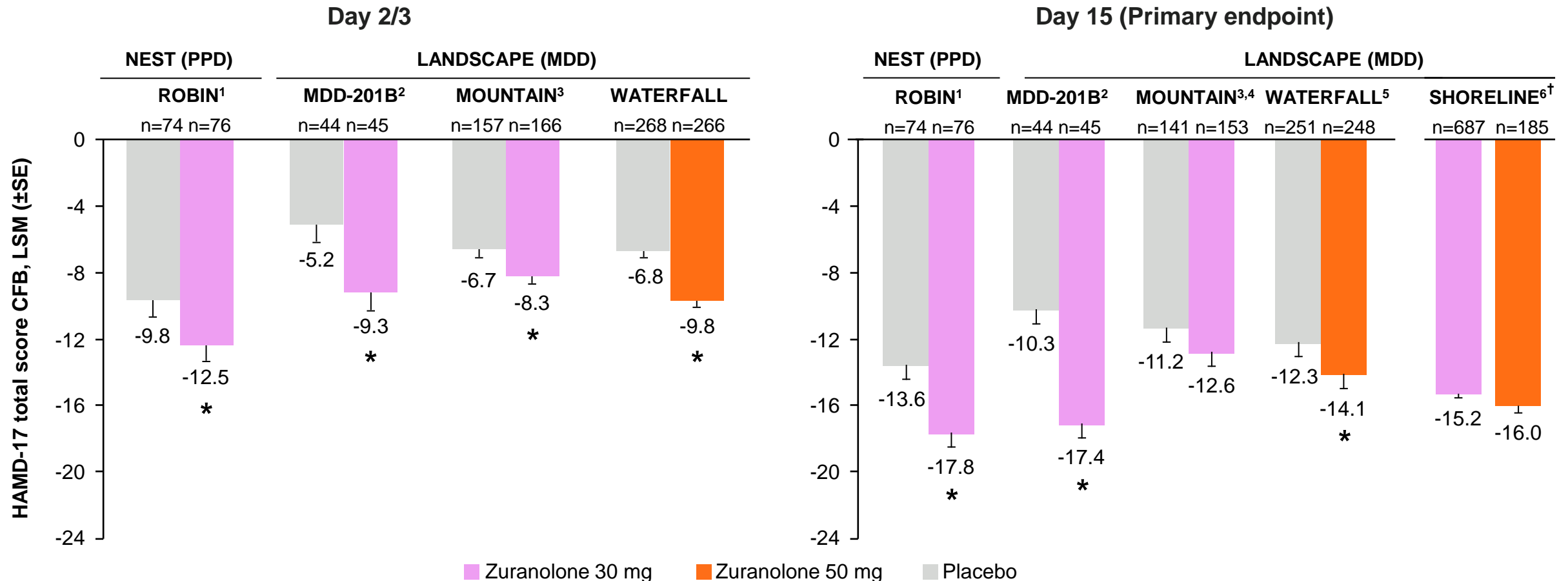
Zuranolone Clinical Development Programs

Potential to reshape the depression landscape



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

Zuranolone has consistently demonstrated rapid improvement in depressive symptoms in clinical trials



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. ROBIN enrolled patients with PPD; MDD-201B, MOUNTAIN, and WATERFALL enrolled patients with MDD. Studies with Day 3 data: ROBIN, MOUNTAIN, WATERFALL; Study with Day 2 data: MDD-201B. The SHORELINE Study is an ongoing, open-label study. In the SHORELINE Study, the Day 15 measurement refers to the initial treatment course and was not the primary endpoint of the study. It was designed to evaluate efficacy in an observational manner only. No statistical inferences can be drawn from the efficacy outcome data.

*p<0.05 vs placebo. p values for Day 2/3 LSM treatment difference are not adjusted for multiplicity and are nominal. †HAMD-17 raw mean change from baseline.

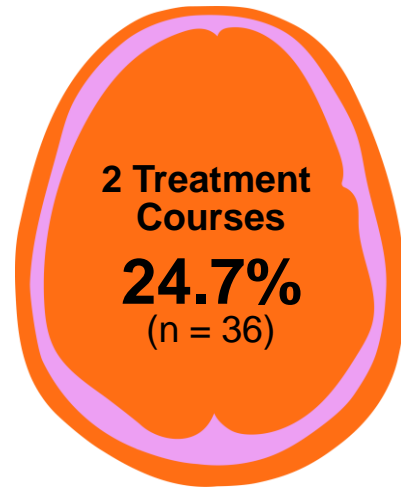
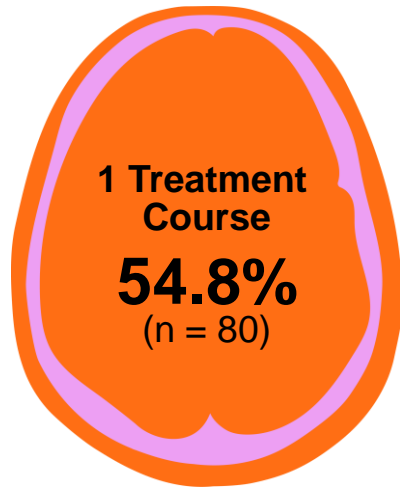
CFB = change from baseline; HAMD-17 = 17-item Hamilton Rating Scale for Depression total score; LSM = least squares mean; MDD = major depressive disorder; PPD = postpartum depression. 1. Deligiannidis KM et al. *JAMA Psychiatry*. 2021 Sep 1;78(9):951-959. 2. Gunduz-Bruce H et al. *N Engl J Med*. 2019;381(10):903-911. 3. Mittal A, et al. Poster presented at the American Academy of Neurology Annual Meeting. Toronto, Canada. April 25-May 1, 2020. 4. Data on file. 217-MDD-301 MOUNTAIN CSR. 5. Clayton A, et al. Oral presentation at the European College of Neuropsychopharmacology Annual Meeting (New Medications Symposium). 2021. 6. Lasser R, et al. Poster presented at: Psych Congress Annual Meeting; 29 Oct-1 Nov 2021; San Antonio, TX. 6. Cutler AJ, et al. Poster presented at: The Society of Biological Psychiatry Annual Meeting; 2021. Zuranolone is being developed in collaboration with Biogen.

Zuranolone demonstrated sustained effects in the SHORELINE Study

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

 **50 mg***

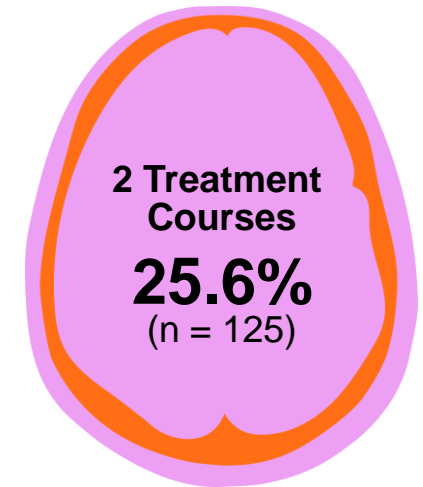
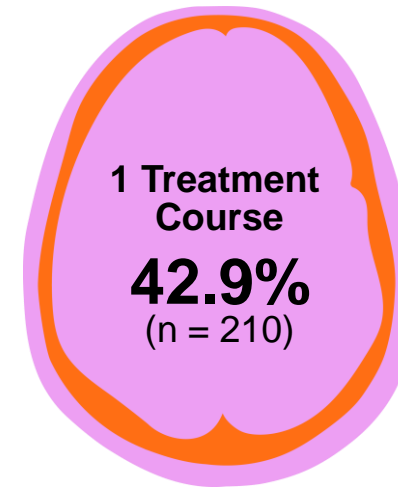
~80% of patients who responded to initial course received 1 or 2 treatment courses



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



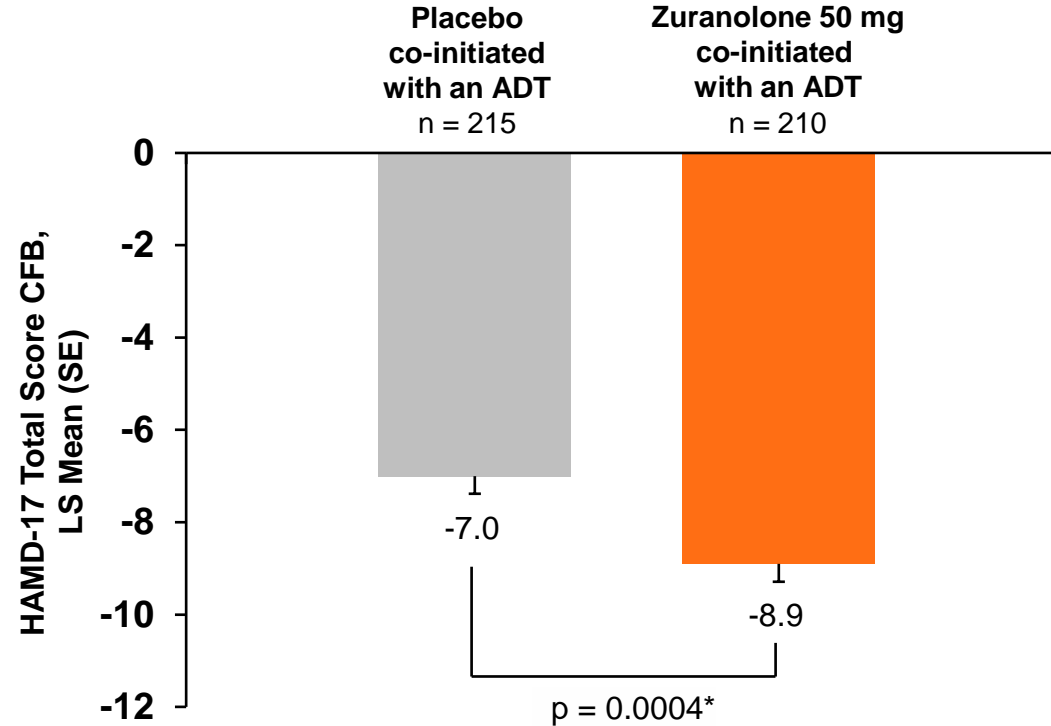
3 Treatment Courses	4 Treatment Courses	5 Treatment Courses
11.9% (n = 58)	10.8% (n = 53)	8.8% (n = 43)

- 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 SHORELINE Study was designed to evaluate efficacy in an observational manner, and therefore, statistical inferences cannot be drawn from efficacy outcome data.²

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 Society of Biological Psychiatry Annual Meeting, 2021 Virtual Meeting; April 29-May 1, 2021.

CORAL Study: Day 3 Primary Endpoint Result

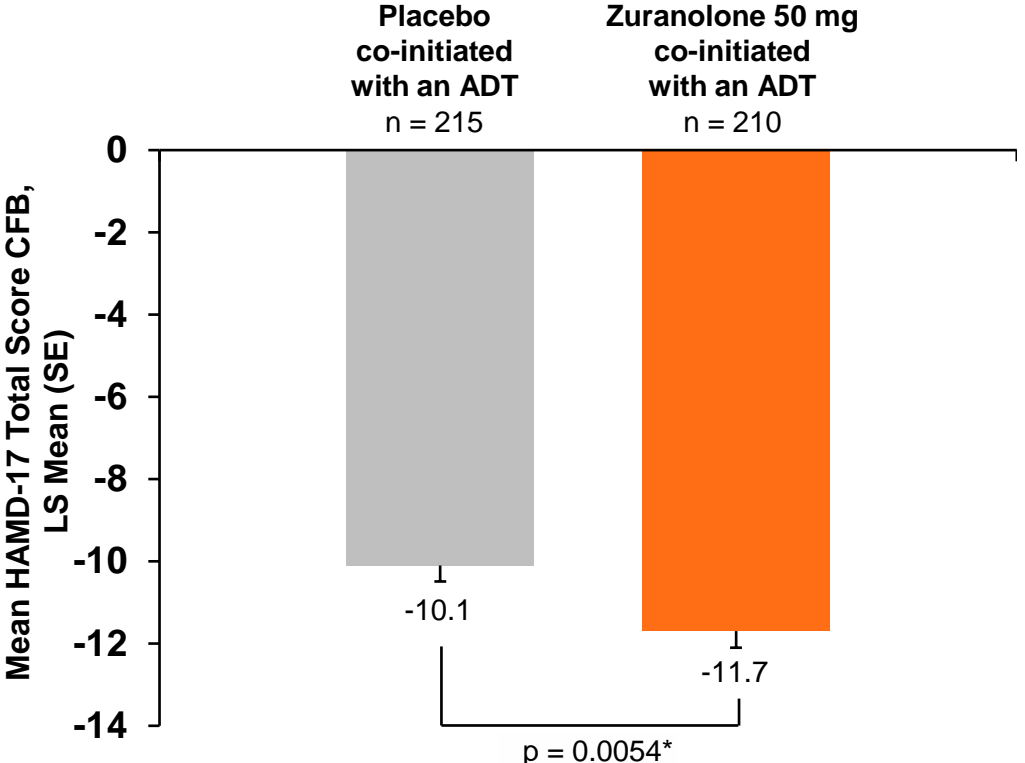


***The primary endpoint (Day 3) was statistically significant at a two-sided 0.05 level of significance under strong control of family-wise error rate.**

†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. Data on file. Topline Results Memo; CORAL: 217-MDD-305. Feb 2022. 2. CORAL Press Release. Feb 2022. <https://investor.sagerx.com/press-releases/>.

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}

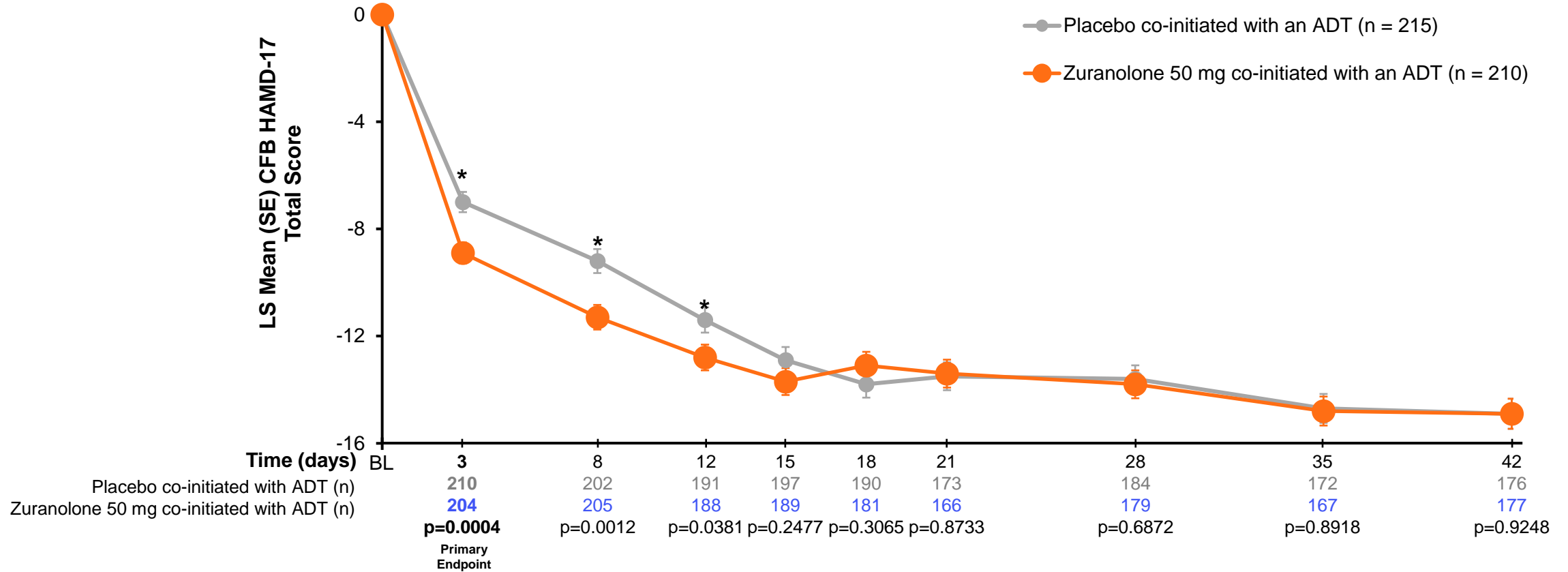
Day	Placebo co-initiated with an ADT (n = 215)	Zuranolone 50 mg co-initiated with an ADT (n = 210)	p value [§]
	LS Mean HAMD-17 Total Score CFB	LS Mean HAMD-17 Total Score CFB	
3 [‡]	-7.0	-8.9	0.0004
8	-9.2	-11.3	0.0012
12	-11.4	-12.8	0.0381
15	-12.9	-13.7	0.2477

[§]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.**

*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. Data on file. Topline Results Memo; CORAL: 217-MDD-305. Feb 2022. 2. CORAL Press Release. Feb 2022. <https://investor.sagerx.com/press-releases/>.

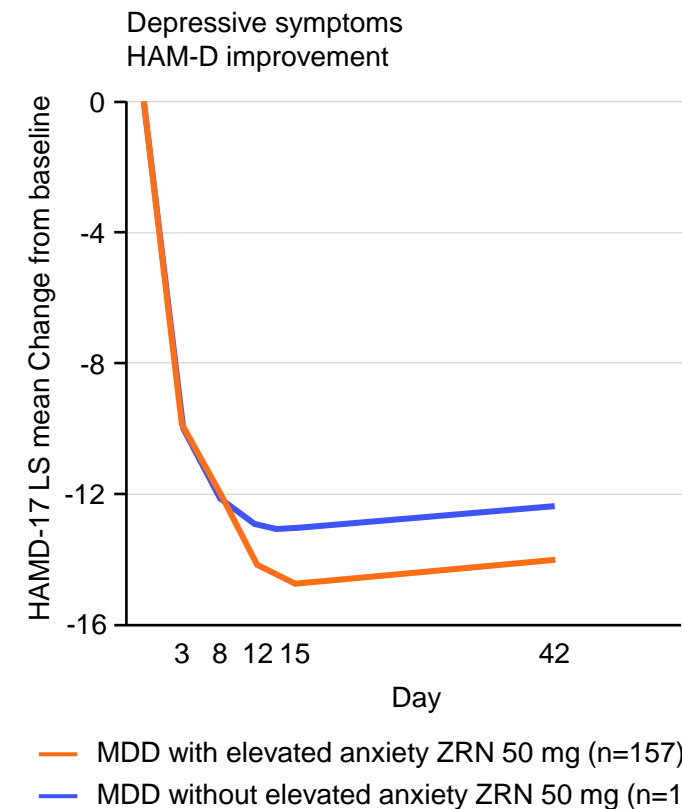
CORAL Study: CFB in HAMD-17 Total Score at Each Time Point in the Study Period by Treatment Group (FAS)



Zuranolone has the potential to address MDD patient populations for whom standard of care doesn't fully address unmet need

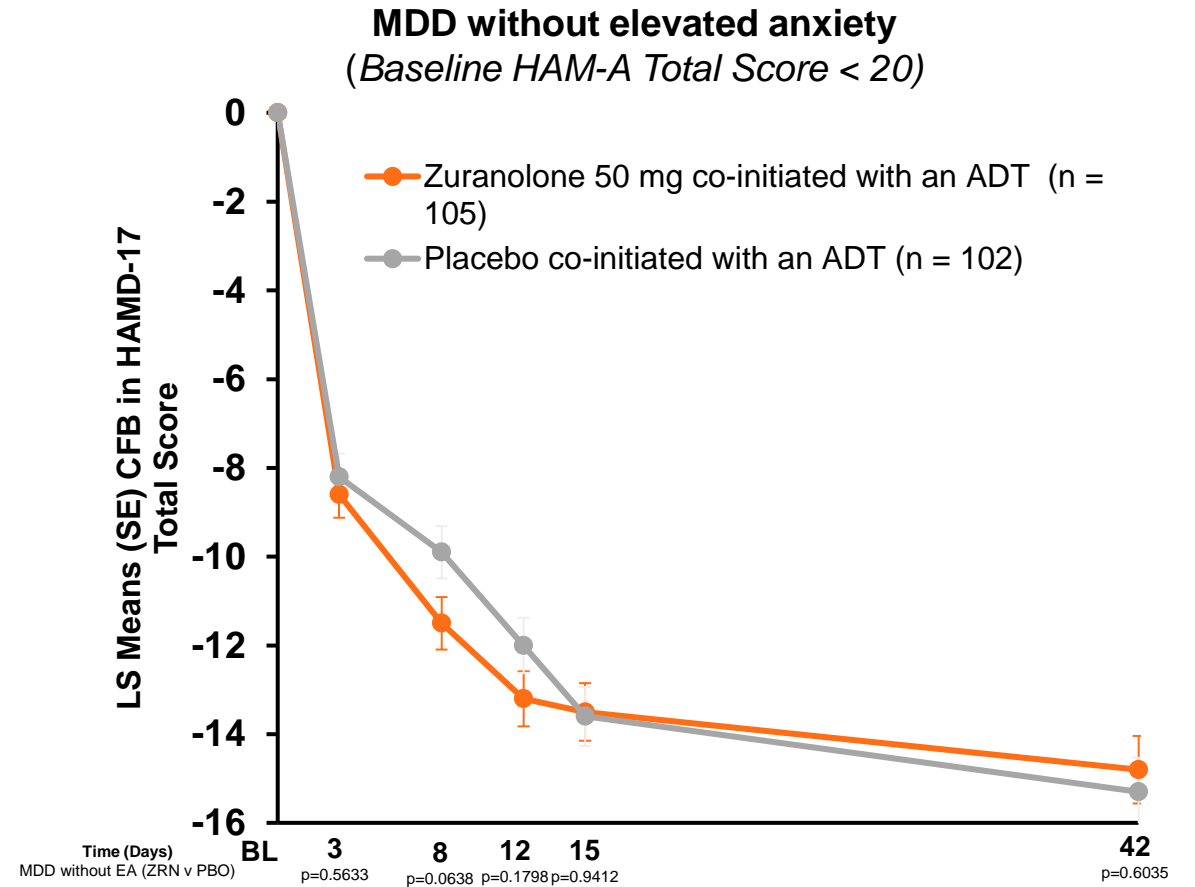
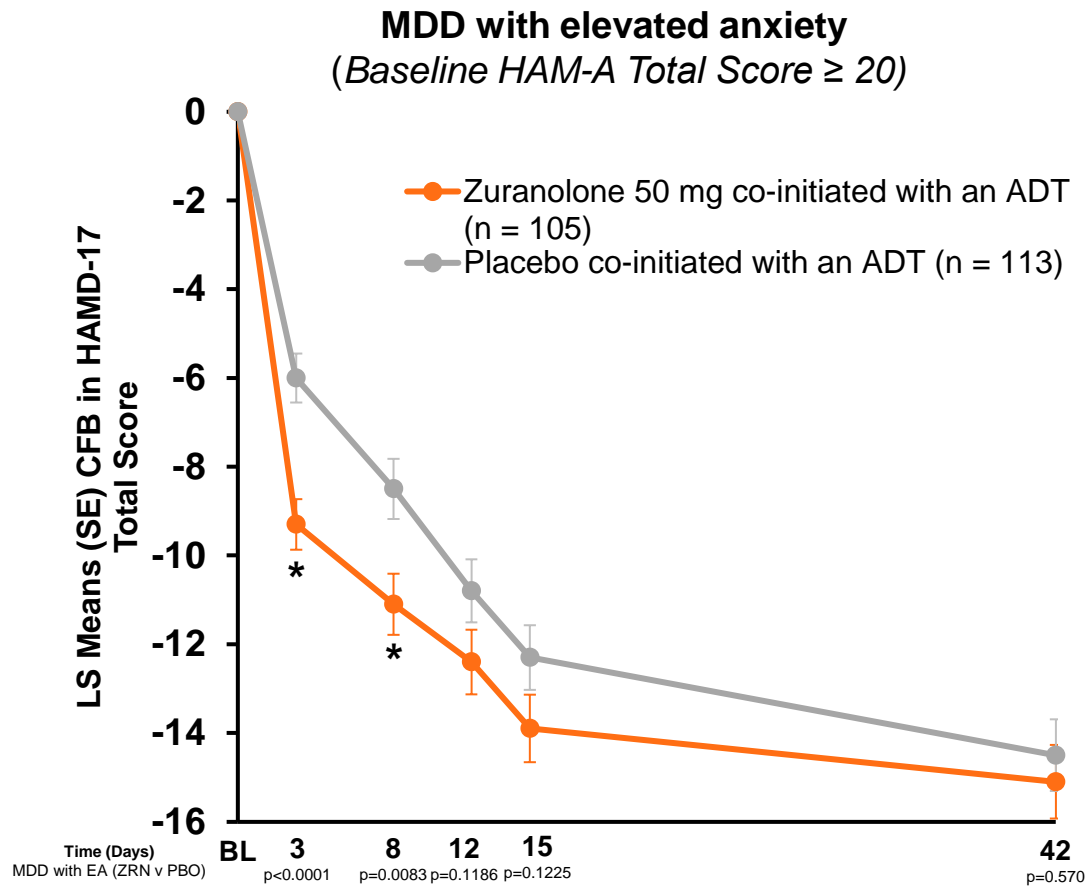
- Continued unmet need evidenced by majority of LANDSCAPE program participants meeting criteria for MDD with elevated anxiety
 - Assessed at baseline by elevated anxiety and somatization symptoms in the setting of MDD (e.g., HAM-D-17, HAM-A scales)
 - Improvements in depression and anxiety symptoms observed 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



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



Short Form-36 Patient Reported Outcome Health Survey

What is SF-36?¹

- SF-36 is 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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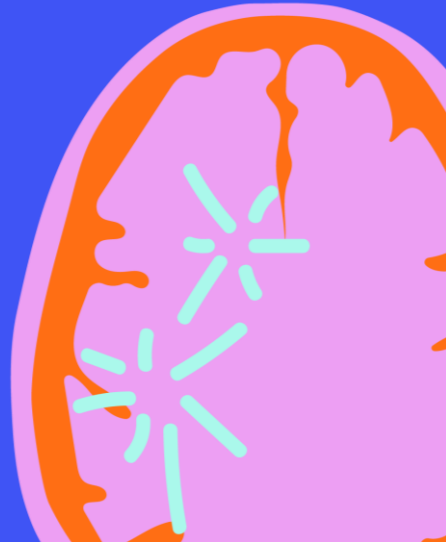
Zuranolone demonstrated improvements across domains of quality of life in clinical trials

LANDSCAPE and NEST integrated SF-36 patient-reported outcome of functioning and well-being[†]

~40-60%

improvement in mental health domains

- Vitality
- Social Functioning
- Role-Emotional
- Mental Health



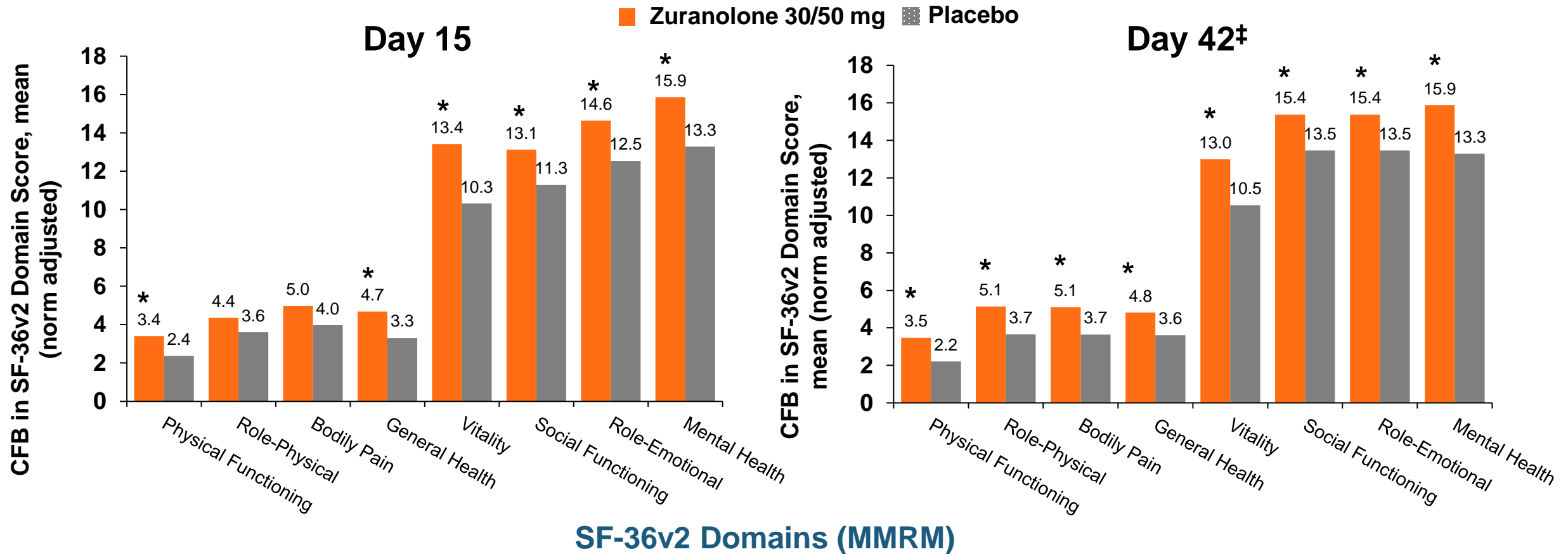
~8-12%

improvement in physical and general health domains

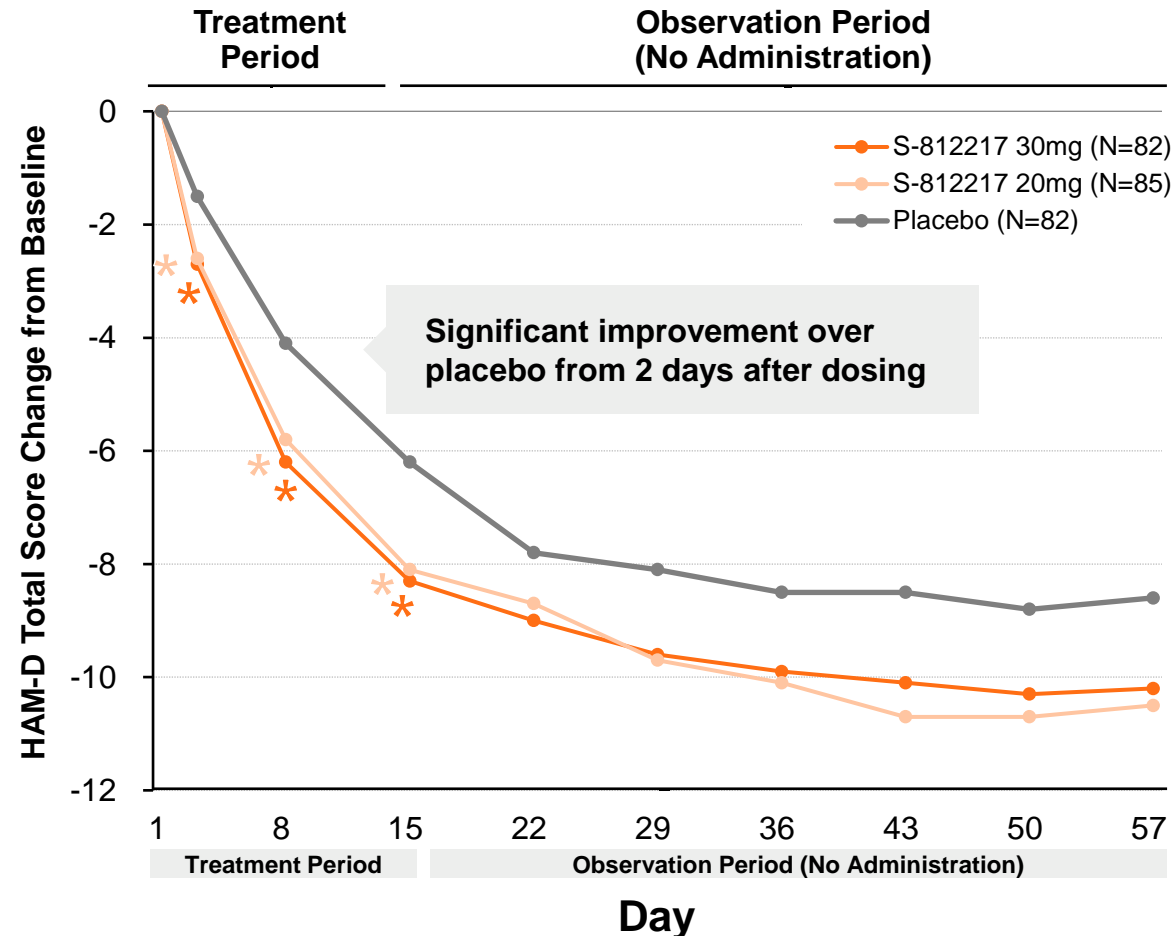
- Physical Functioning
- Role-Physical
- Bodily Pain
- General Health



NEST/LANDSCAPE: Integrated SF-36 Patient-Reported Outcome of Functioning and Well-Being[†]



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



Efficacy

- **Achieved the primary endpoints 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



Zuranolone has demonstrated a consistent and differentiated tolerability profile in clinical trials

“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

- The most common TEAEs* across zuranolone studies^ were headache (6-18%), somnolence (7-16%), dizziness (6-15%), nausea (4-11%), sedation (4-10%), URTI (1-8%†), diarrhea (0-7%), insomnia (7%†), fatigue (7%‡), dry mouth (4-6%), tremor (5%†)
- Most TEAEs across the zuranolone clinical development program were mild or moderate in severity
- Discontinuation rates due to AEs of less than or equal to 6.5% across controlled and uncontrolled studies

CORAL Study: Safety/Tolerability through Day 42

- Over the study period, TEAEs $\geq 10\%$ 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 ($\geq 10\%$ in either treatment group) through Day 42^{1,2}

	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. Data on file. Topline Results Memo; CORAL: 217-MDD-305. Feb 2022. 2. CORAL Press Release. Feb 2022. <https://investor.sagerx.com/press-releases/>.

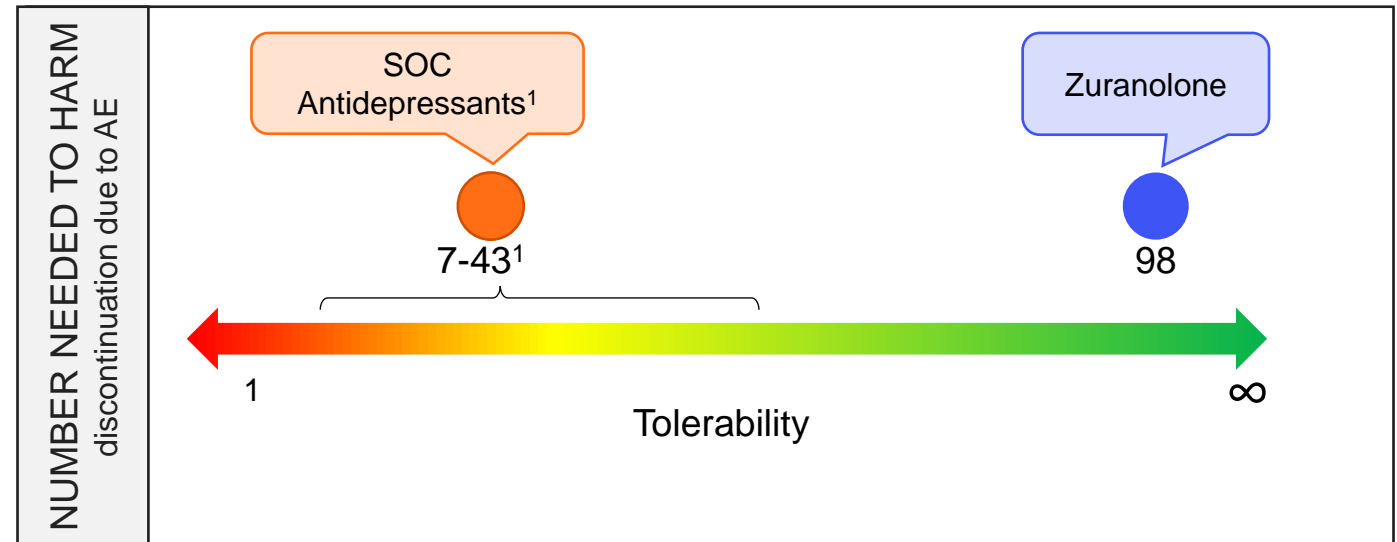
Zuranolone is being developed in collaboration with Biogen.

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

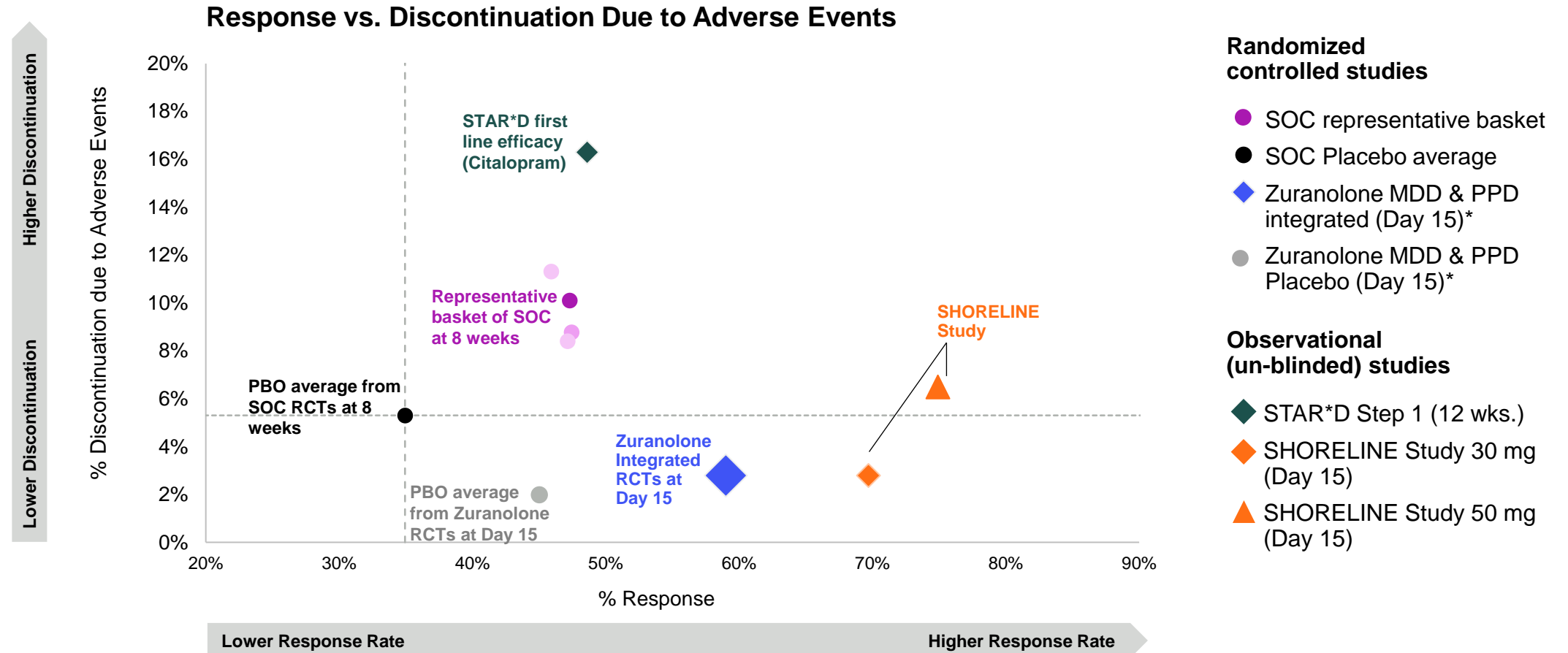
Discontinuation due to adverse event rates		
	Placebo	Zuranolone (30mg and 50mg)
MDD-201B	0.0%	4.4%
ROBIN Study	0.0%	1.3%
MOUNTAIN Study	3.2%	2.1%
WATERFALL Study	1.5%	3.4%
Weighted average (by n)	1.7%	2.8%



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



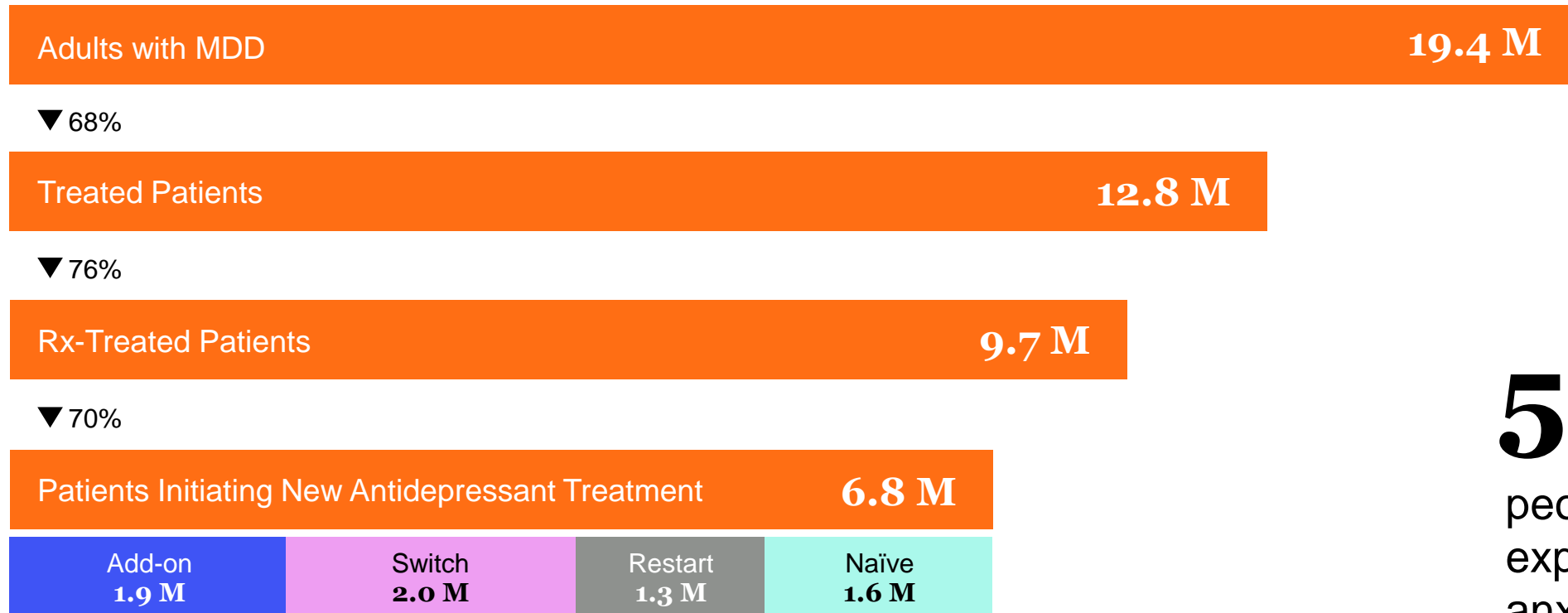
- Methods: Average response (>50% reduction from baseline) and discontinuation due to side effects rates for SOC were obtained from Cipriani et al. 2018 (average placebo for SOC trials and representative basket of SOC products), and for zuranolone from an integrated analysis of zuranolone clinical data; 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.

Sage's planned commercialization approach designed to educate and engage stakeholders

Stakeholder Needs	Strategic Imperatives
<p>Patients</p> <p>Rapid, durable therapy without stigmatizing side effects often associated with chronic treatments (e.g., sexual dysfunction/weight gain)</p>	<p>▶ Inspire people with MDD and PPD to talk to their HCP about zuranolone</p>
<p>HCPs</p> <p>Rapid, durable, well-tolerated therapy for a range of patients with MDD and PPD with low/no access hurdles</p>	<p>▶ Mobilize targeted HCPs to identify and treat zuranolone patient types in MDD and PPD</p>
<p>Payors</p> <p>Efficacious, cost-effective solution for MDD and PPD patient types associated with poorer outcomes</p>	<p>▶ Connect treatment outcomes in MDD and PPD with zuranolone performance through innovative proactive Value Based Agreements to drive at-launch access</p>
<p>Patient Advocacy and Policy Makers</p> <p>Education to advocate for and advance the standard of care for those who need more from MDD and PPD treatment</p>	<p>▶ Raise treatment expectations in MDD and PPD through grassroots efforts, leveraging policy interventions that have been proven effective in addressing access to treatment</p>

The MDD landscape presents significant opportunity for a new therapy to help patients at various points in their treatment journey

MDD Patient Opportunity



54-66%
people with MDD also experience elevated anxiety symptoms



Potential clinical use scenarios for zuranolone in MDD



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

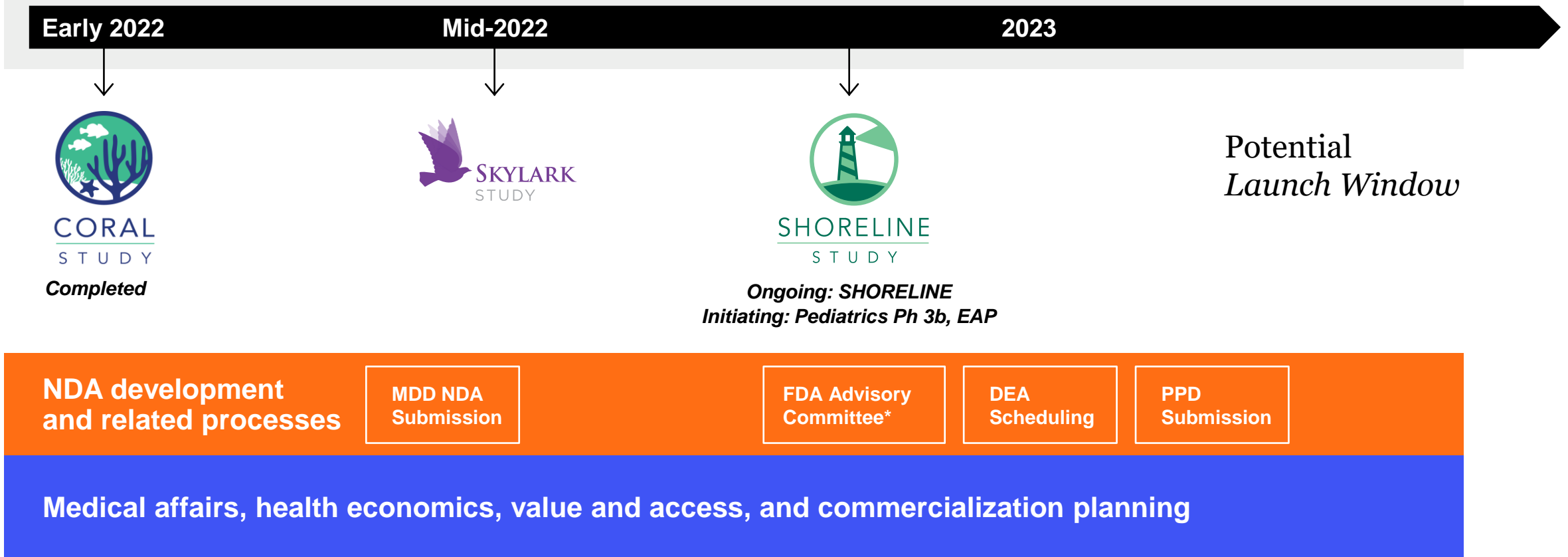
“Major depressive disorder with elevated anxiety is a common presentation of depression and is associated with a more prolonged and severe disease course and poor response to current treatments. Data from the LANDSCAPE and NEST clinical development programs indicate that, if approved, zuranolone may 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 MGH Executive Committee on Research
Executive Director, Clinical Trials Network and Institute, Massachusetts General Hospital (MGH)
Associate Dean for Clinical and Translational Research, Slater Family Professor of Psychiatry,
Harvard Medical School

Zuranolone development plans over next 24 months include two Phase 3 readouts and NDA submissions

Planned activities and anticipated timelines



Upcoming zuranolone, MDD data presentations & next steps

- **Sage is committed to sharing data from the LANDSCAPE and NEST clinical development programs as well as supportive real-world evidence at premier scientific forums, potentially including:**
 - Efficacy and safety data that support the potential for rapid onset and sustained effect of zuranolone 30 and 50 mg from the SHORELINE & WATERFALL Studies
 - Patient reported outcomes that may support clinical understanding of zuranolone in the treatment of depressive symptoms
 - Impact of delayed treatment on the course of MDD
 - Real world evidence on the societal impact of MDD

Potential congresses for data presentations include:

- European College of Neuropsychopharmacology 35th Annual Congress
- Psych Congress
- American College of Neuropsychopharmacology 60th Annual Meeting
- Society of Biological Psychiatry Annual Meeting
- American Psychiatric Association Annual Meeting
- American Academy of Neurology Annual Meeting
- American Society of Clinical Psychopharmacology Annual Meeting
- European Psychiatric Association 30th Congress

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

Huntington's Disease

~8.8M

Parkinson's Disease

~134M

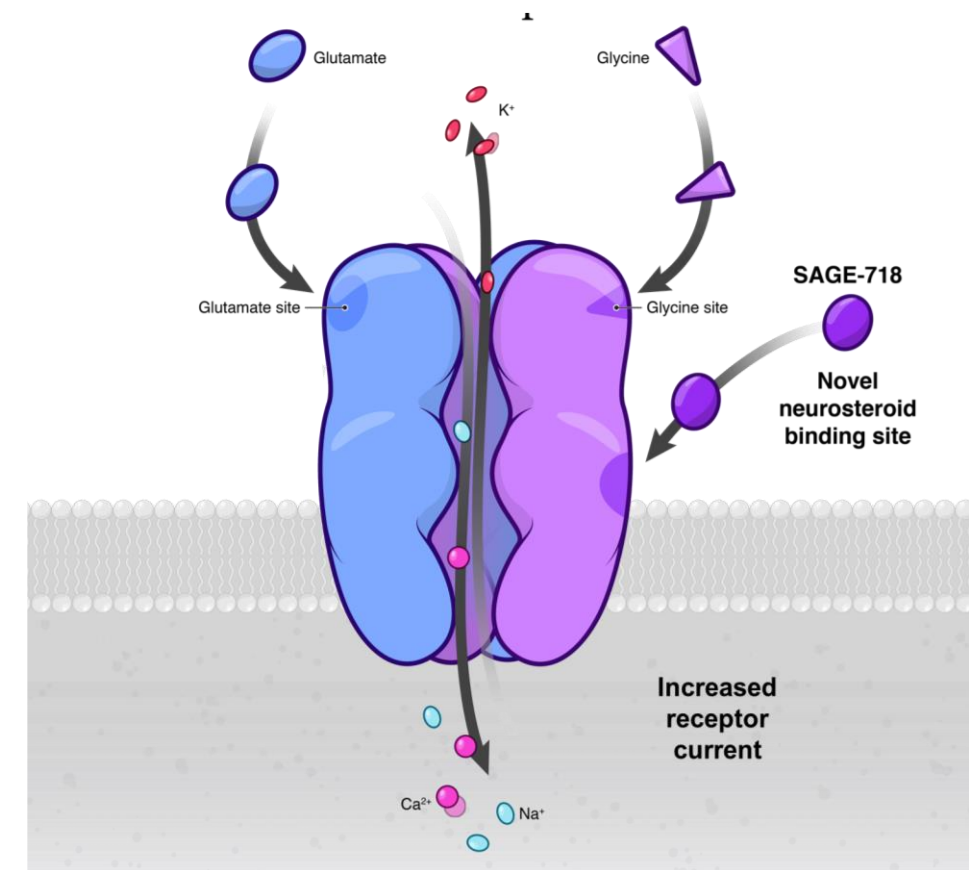
Alzheimer's Disease

Re-thinking treatment of neuropsychiatric disorders

Sage has developed a robust library of NMDA receptor modulators

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

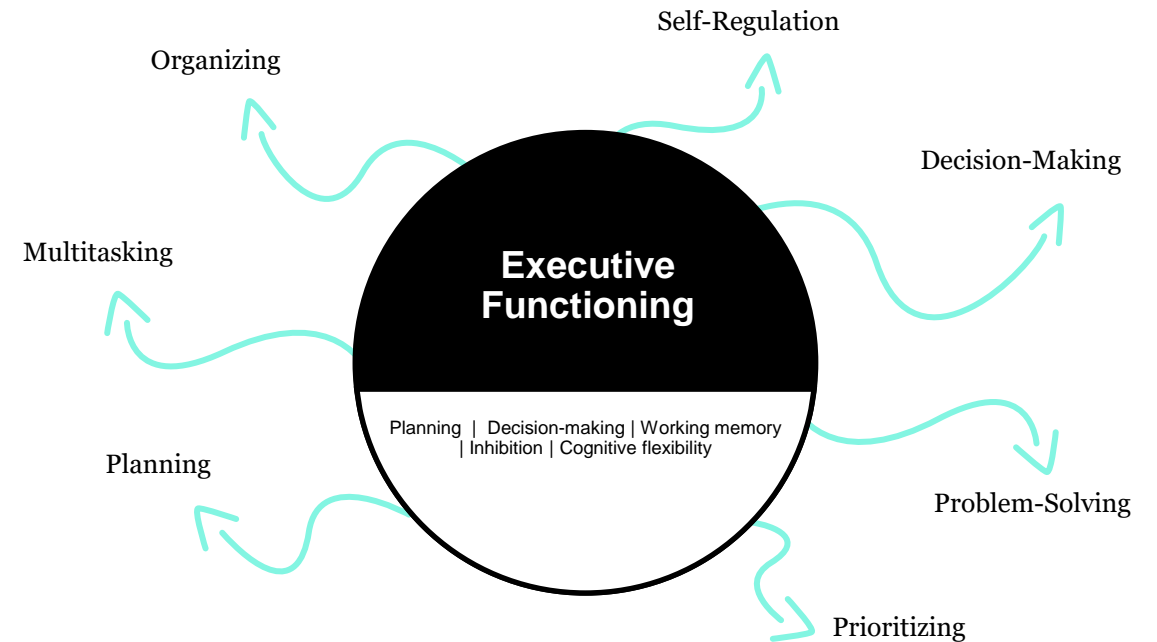
Endogenous & Exogenous Ligands at the NMDA Receptor



SAGE-718: Improving cognitive and executive function

Potential to provide unique cognitive benefits for patients with neurodegenerative disorders

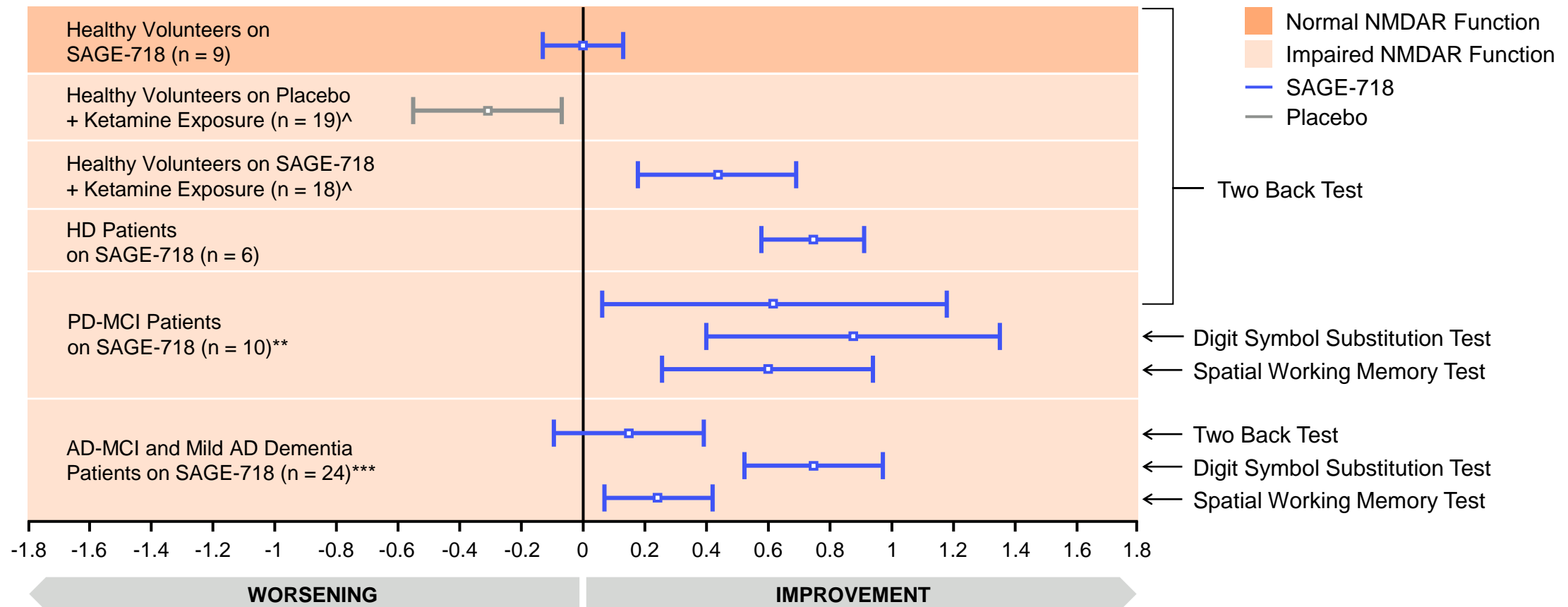
- SAGE-718 profile well-suited for study of potential to benefit executive function in patients with neurodegenerative disorders:
 - Clinical findings from Phase 1 studies suggest potential to improve executive function, a key component of brain health across life-span
- Ongoing exploration in areas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



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 2-back, and day 28 for PD/AD DSST and SWM

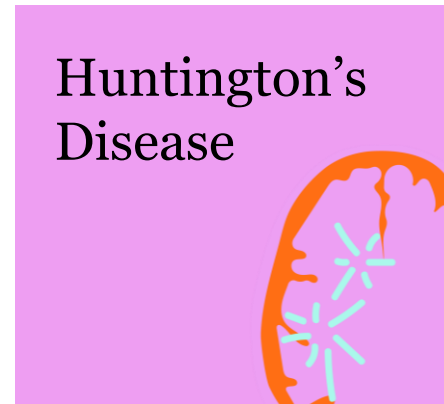
**n=6 for Two-Back, n=9 for DDST

***n=21 for Two-Back, n=23 for SWM

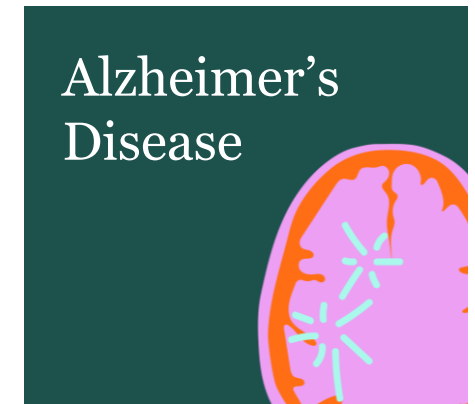
SAGE-718 clinical development program designed with goal to de-risk opportunities in multiple indications

- 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
- Plans for further development including in Parkinson's and Alzheimer's disease
- Leveraging learnings across indications designed to help de-risk program

Initial Indication

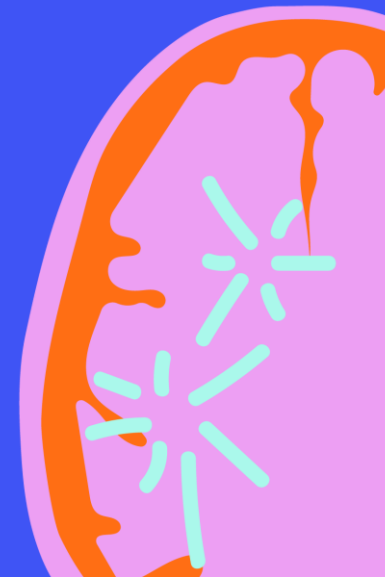
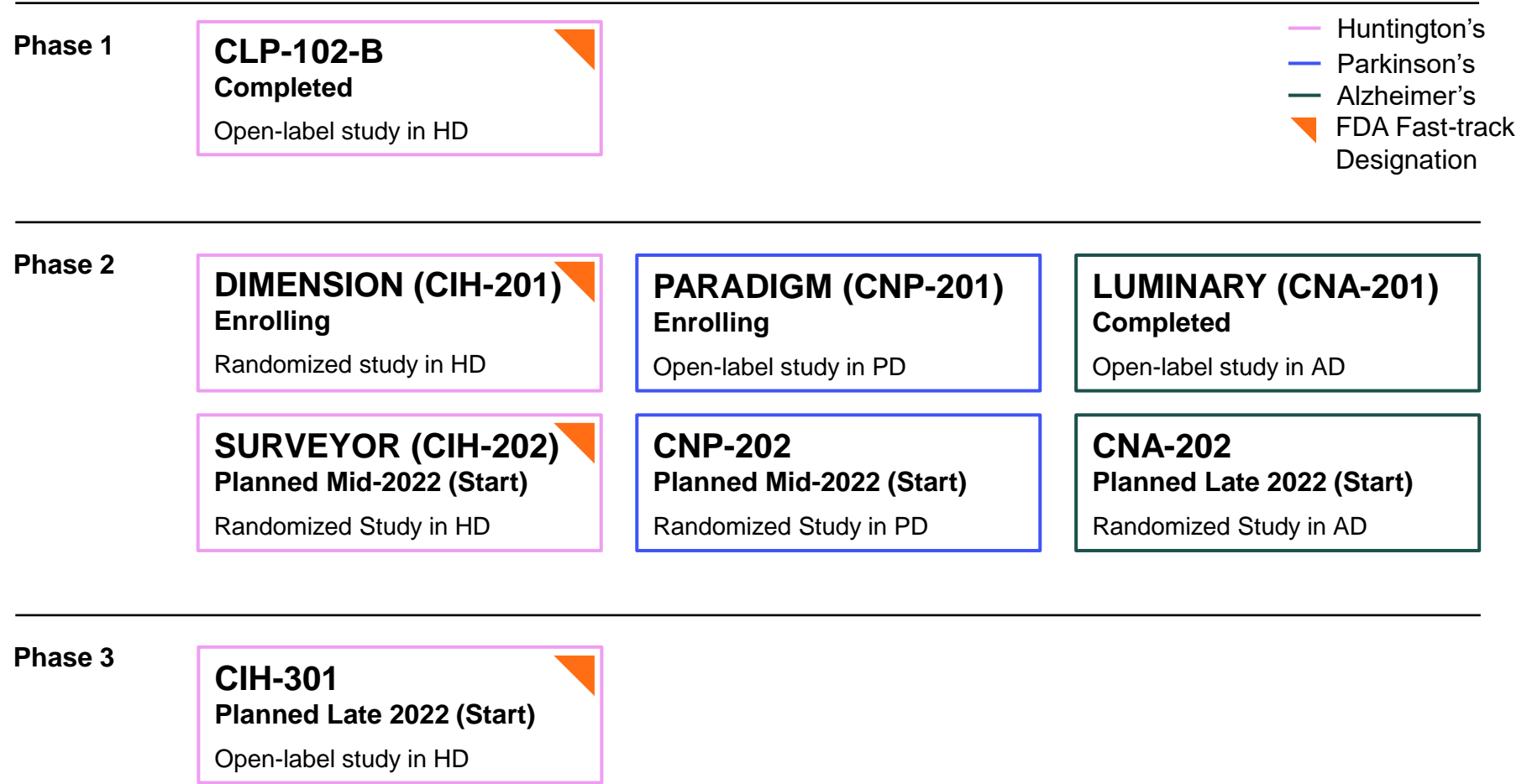


Planned Additional Indications



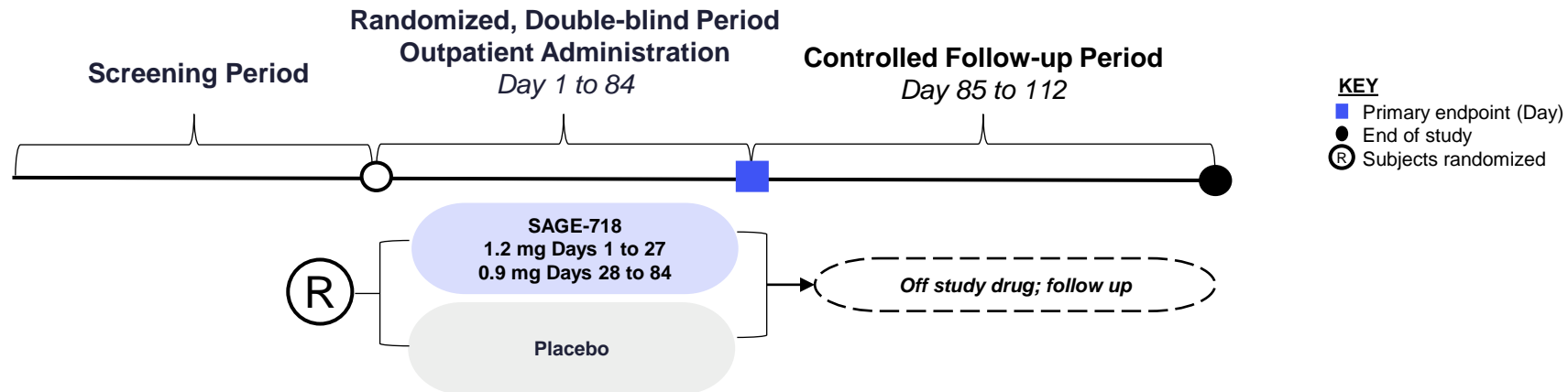
SAGE-718 planned clinical development program designed to define potential benefits and leverage learnings

Huntington's Disease & CogNEXT Clinical Signal-Finding Studies

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		

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

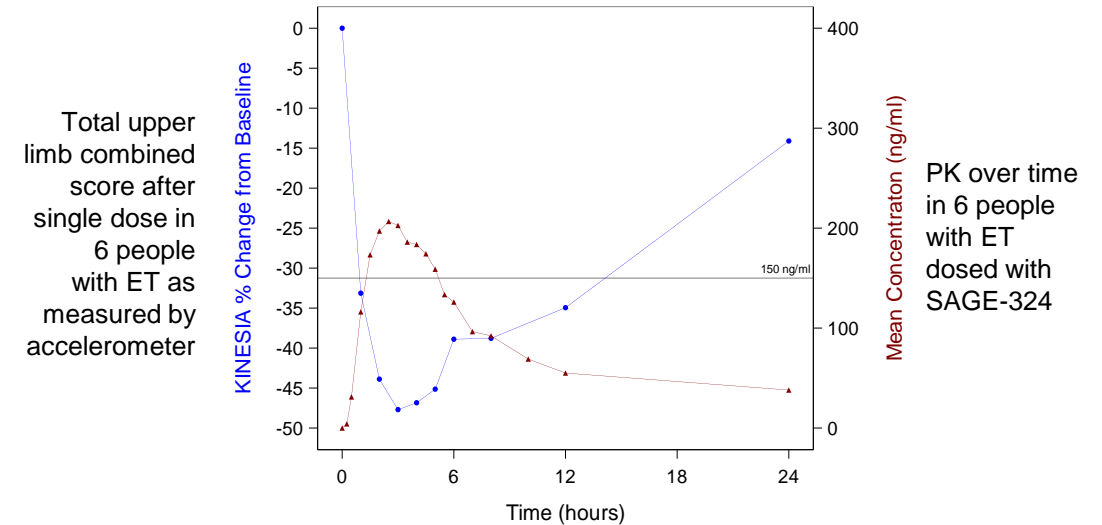
79% of employed patients have reduced hours or changed jobs due to ET

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

SAGE-324: Novel potential treatment for movement disorders

Predictable PD effects and PK profile with long half-life

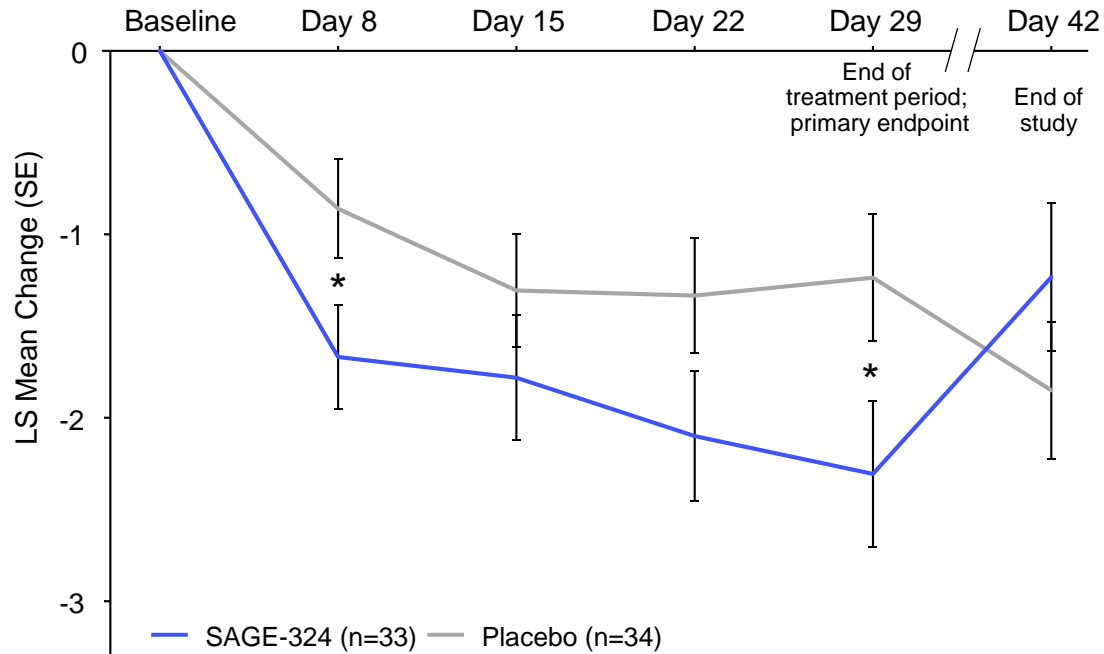
- SAGE-324 is well-suited for development in essential tremor (ET):
 - Most prevalent movement disorder in the US (est. 6M+)
 - Last pharmacological treatment for ET was approved in 1967
 - High unmet need; 50% of treated patients do not respond or have sub-optimal response to standard of care
- In an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

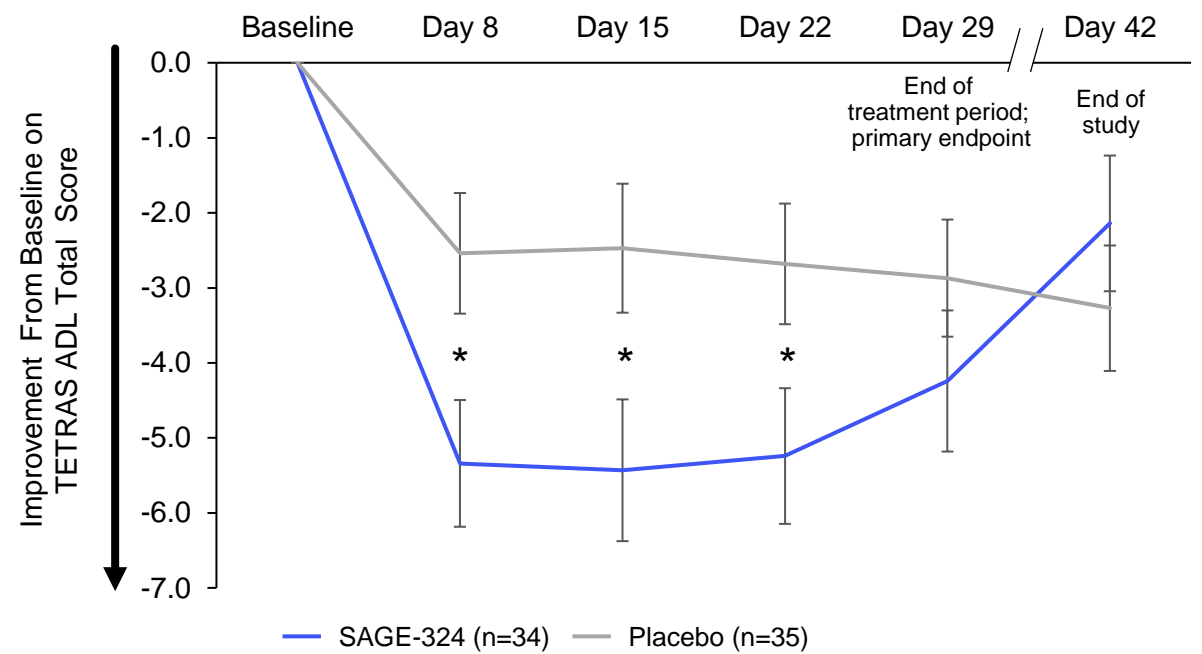
Improvement in tremor control and ADL score observed in the KINETIC Study

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)

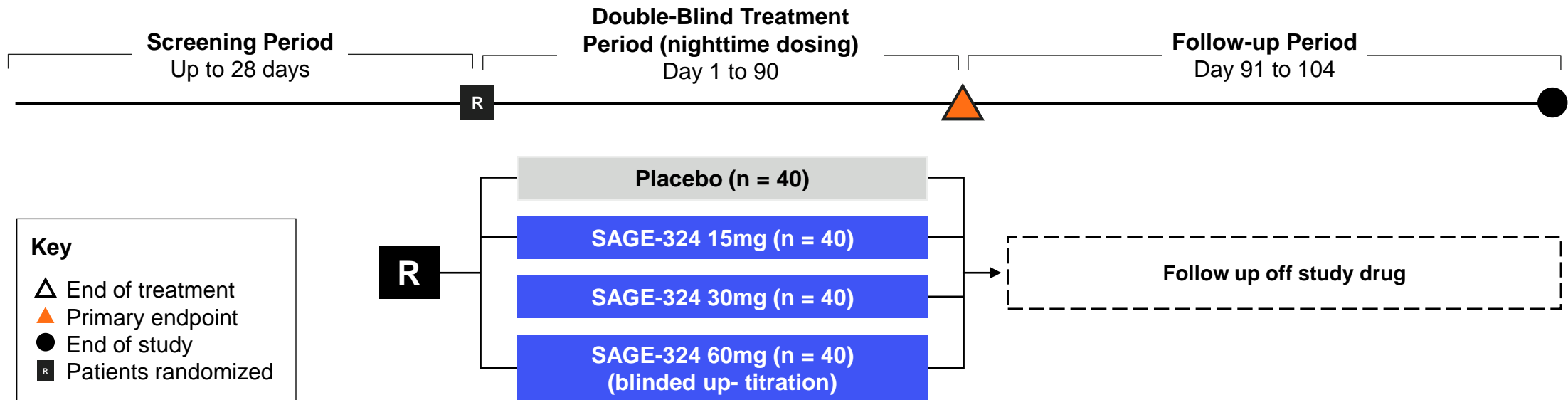
Change From Baseline for TETRAS ADL Subscale Total Score in SAGE-324 and Placebo Treatment Groups



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%).

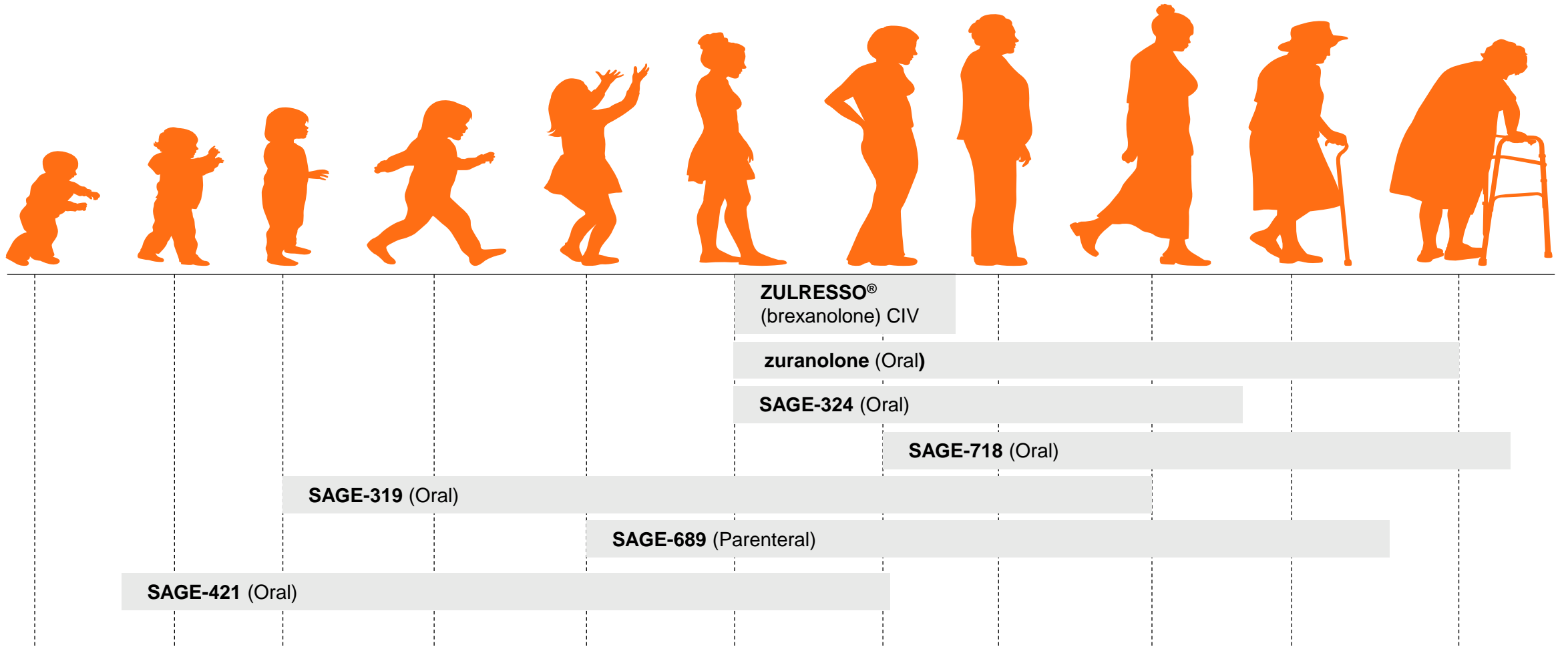
324-ETD-202: Phase 2 double-blind, randomized, placebo-controlled, dose–response study of SAGE-324 for the treatment of patients with essential tremor



- 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 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

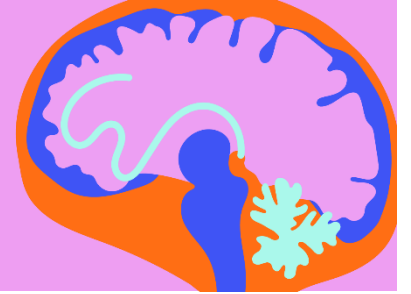


- Extra-synaptic GABA_A receptor preferring positive allosteric modulator
- Profile supporting daily, oral, chronic dosing
- Differentiated preclinical EEG signature compared to zuranolone and SAGE-324

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

Fourth Quarter and Full Year 2021 and 2020 Financial Results

Strong financial position with over \$1.7B in cash; 2020, the revenue was mainly related to the collaboration with Biogen

Item	Q4 '21	Q4 '20	Full Year '21	Full Year '20
Revenue	\$1.6M	\$1.1B	\$6.3M	\$1.1B
R&D Expense	\$75.4M	\$81.7M	\$283.2M	\$292.7M
SG&A Expense	\$51.6M	\$53.5M	\$183.5M	\$197.0M
Cost of Goods Sold	\$0.1M	\$0.1M	\$0.6M	\$0.6M
Restructuring	-	(\$0.1M)	-	\$27.7M
Total Operating Costs and Expenses	\$127.1M	\$135.2M	\$467.2M	\$518.0M
Net Income (Loss)	(\$124.7M)	\$974.9M	(\$457.9M)	\$606.1M
Cash and Marketable Securities	\$1.7B	\$2.1B	\$1.7B	\$2.1B

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
	●	●		Rolling submission of NDA filing package for the treatment of MDD
		●		Report topline data from SKYLARK Study in PPD
			●	Submit NDA filing package for the treatment of MDD (2H 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
			●	Complete enrollment in Phase 2b KINETIC 2 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

Data rich 2021 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 four ongoing Phase 2 studies in 2022 and submit NDA filing seeking approval for second marketed product

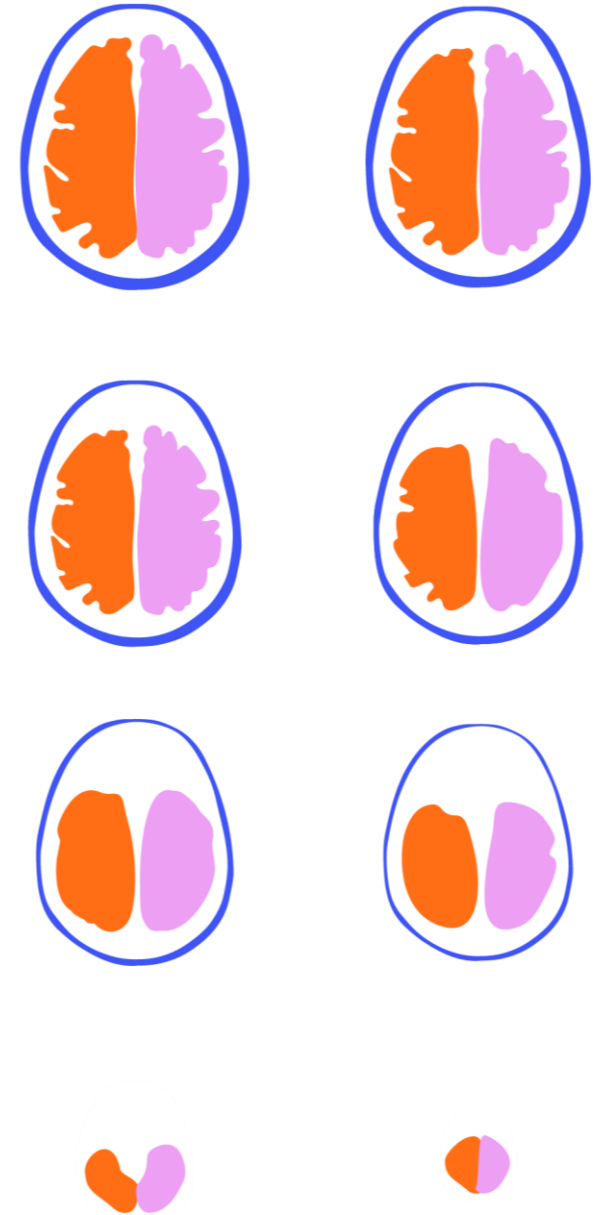
Focused on plans for potential commercialization for later-stage programs

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

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



Brain Health Disorders – Global Healthcare Challenge

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



> 450M

Sage + Shionogi + Biogen
+ potential acceleration of Sage proprietary programs

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

Postpartum Depression		
Major Depressive Disorder		

	Shionogi Collaboration	2020 Biogen Collaboration
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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

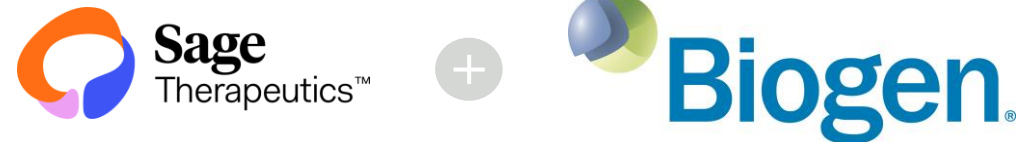
Upfront payment

\$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

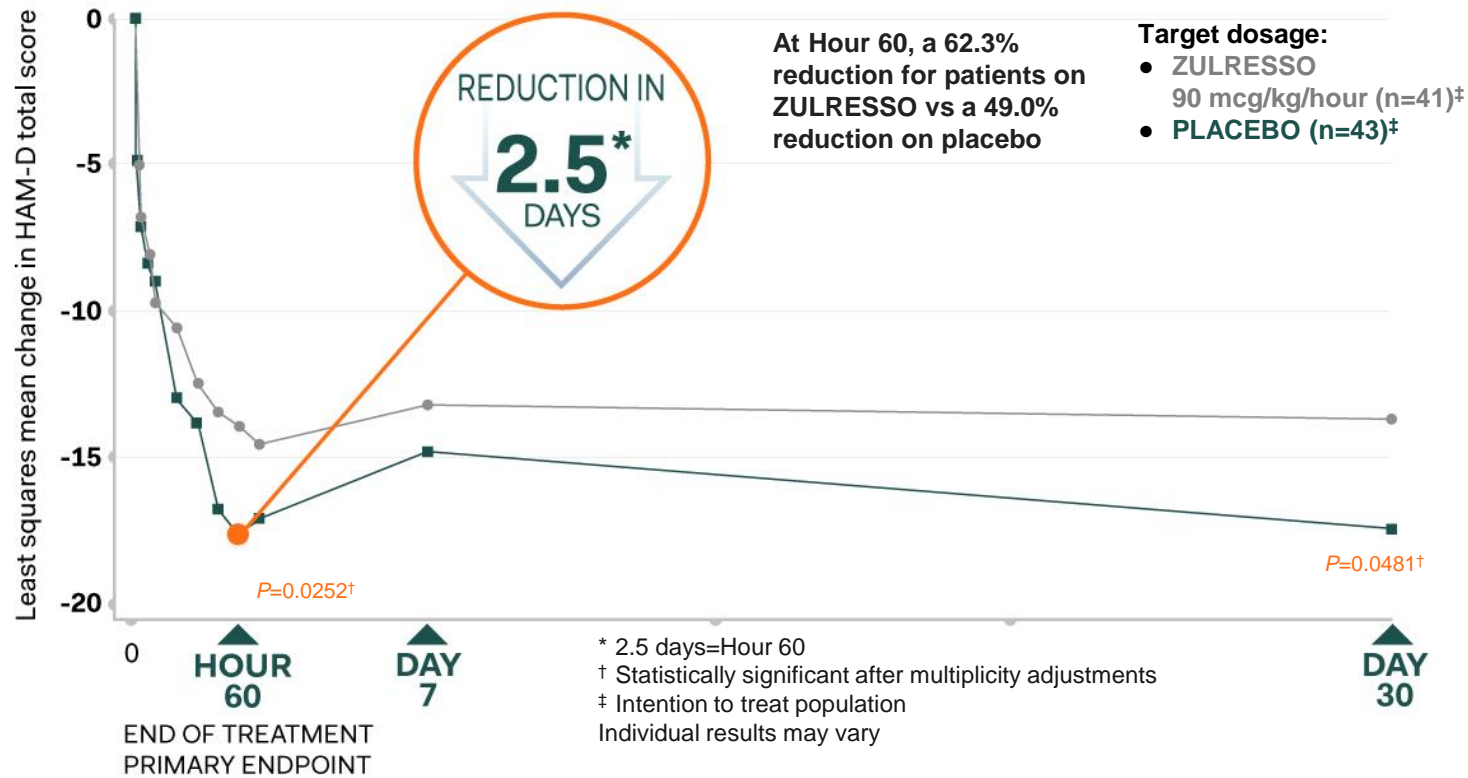
\$1.6B

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 $\geq 5\%$ 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*