CORAL Study (217-MDD-305; NCT04476030) Topline Results:

Phase 3, randomized, double-blind, placebo-controlled study assessing the efficacy and safety of zuranolone 50 mg co-initiated with an antidepressant therapy (ADT) compared to placebo co-initiated with an ADT in adults with major depressive disorder (MDD)

Forward Looking 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 belief in the potential benefit and profile of zuranolone and in its potential to be successful and to meet an unmet need in the treatment of MDD; the potential regulatory pathways for filing and approval of zuranolone, expected timelines for filings and the potential for approval and launch, including anticipated timelines; the potential for commercialization of zuranolone and our commercialization plans; our expectations as to the types of MDD patients who may benefit from zuranolne, if approved; the goals, opportunity, mission and vision for our Company, including our goals for generating new INDs and launching new products or indications and the potential for our business; 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;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; and our vision for our company.

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. 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; we may encounter issues with the efficacy or durability of short-term treatment, or co-initiated treatment with zuranolone or safety and efficacy concerns with respect to retreatment that require additional studies be conducted;
- The FDA and other regulatory authorities may ultimately decide that the design or results of our completed, ongoing or planned clinical trials for 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. 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 INDs or new products or new indications from our research and development efforts that we expect in the future. We may not be successful in our goal to become the leading brain health company or a top tier biopharmaceutical company.
- 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 or on the terms we expect. 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 our 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. We may need or choose to raise additional funding, which may not be available on acceptable terms, or at all.
- We may not be able to establish and maintain key business relationships with third parties on acceptable terms or we may encounter problems with the performance of such third parties.
- We may encounter technical and other unexpected hurdles in the manufacture and development of our products.
- Any of the foregoing or other factors may negatively impact our ability to achieve our goals, mission, opportunities, plans or expectations for our business.

For additional disclosure regarding these and other risks Sage faces, see the disclosure contained in the "Risk Factors" section of our most recent report, and in our other public filings, with the Securities and Exchange Commission, available on the SEC's website at http://www.sec.gov. Any forward-looking statement represent our views only as of today, and should not be relied upon as representing our views as of any subsequent date. We undertake no obligation to update or revise the information contained in this presentation, whether as a result of new information, future events or circumstances or otherwise.

Sage Therapeutics®

Sage'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
- 7 clinical phase NCE development programs across 12+ 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

$1.8B+ capital/collaborations to fund efforts to accelerate and advance medicines

Potential to impact an estimated >450M patients globally

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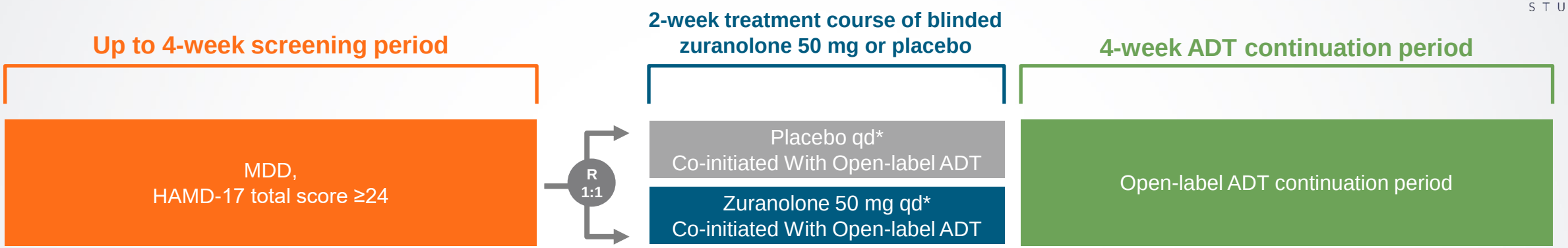
CORAL Study Design[1,2]



Study Design Elements:

- Phase 3, randomized, double-blind study (NCT04476030).[1]
  - **Treatment course** = 14 days of dosing with zuranolone 50 mg co-initiated with an ADT or placebo co-initiated with an ADT.[2]
  - **Treatment period** = time from first dose to last dose of zuranolone 50 mg co-initiated with an ADT or placebo co-initiated with an ADT in a 2-week treatment course plus 1 day (Day 15).[2]
  - **Study period** = 2-week treatment course plus 4-week open-label ADT continuation period through Day 42 (end of study).[2]
- After completing the CORAL Study, all patients were given the option to rollover into the SHORELINE Study (NCT03864614).[2,3]

Study Population[1]:

- Patients with MDD for at least 4 weeks (baseline HAMD-17 total score ≥24).
- Actual enrollment: N = 440.
- The mean (SD) baseline HAMD-17 score at entry into the study was 26.8 (2.5) in the zuranolone 50 mg co-initiated with ADT arm and 26.6 (2.6) in the ADT co-initiated with placebo arm.

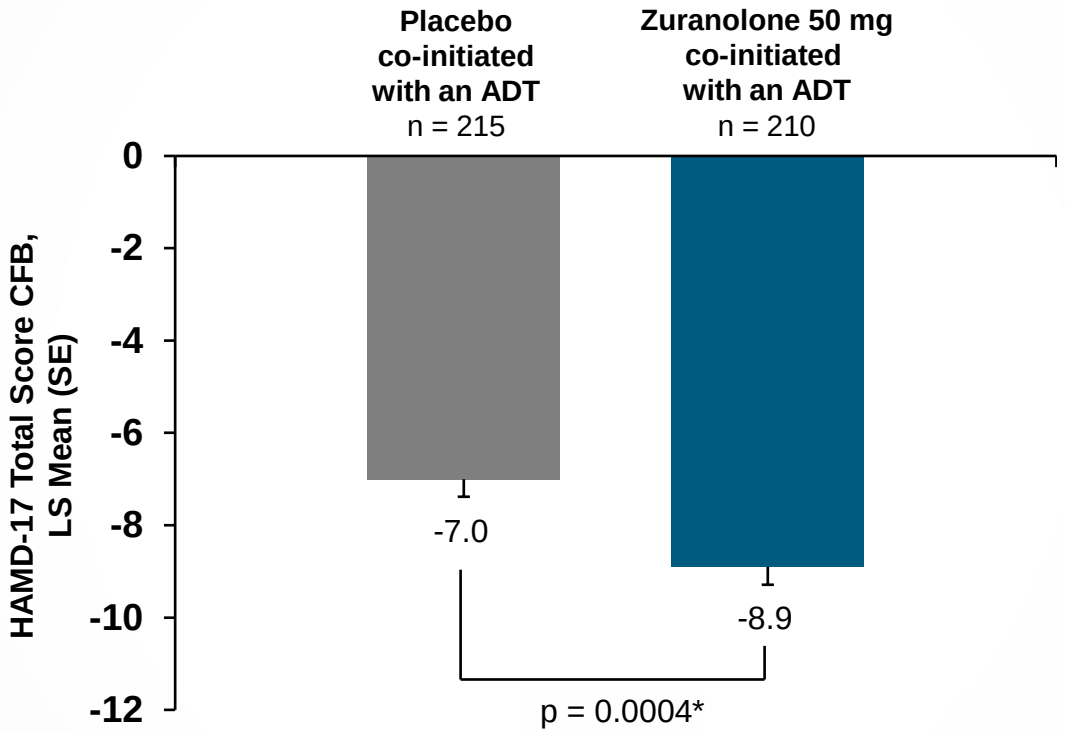
Intervention/Treatment[1,*]:

- Zuranolone 50 mg or matching placebo.
- Both zuranolone 50 mg and placebo groups co-initiated with open-label ADT[†]:
  - Sertraline.
  - Escitalopram.
  - Citalopram.
  - Duloxetine.
  - Desvenlafaxine.

*Zuranolone 50 mg and placebo were administered in the evening with fat-containing food. Down-titration to zuranolone 40 mg was allowed if 50 mg was not tolerated.[2]
[†]Dosing of ADT could be modified as appropriate per the labeled prescribing information and based on individual response.[2]
ADT = antidepressant therapy; HAMD-17 = 17-item Hamilton Rating Scale for Depression; MDD = major depressive disorder; qd = once daily; R = randomization.
1. CORAL. ClinicalTrials.gov Identifier: NCT04476030. 2. Data on file. Protocol 217-MDD-305. Jan 2022. 3. SHORELINE. ClinicalTrials.gov Identifier: NCT03864614.
Zuranolone is being developed in collaboration with Biogen.

CORAL Study: Primary Endpoint Result

LS Mean CFB HAMD-17 total score at Day 3 (*Primary Endpoint*)[1,2,†]



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

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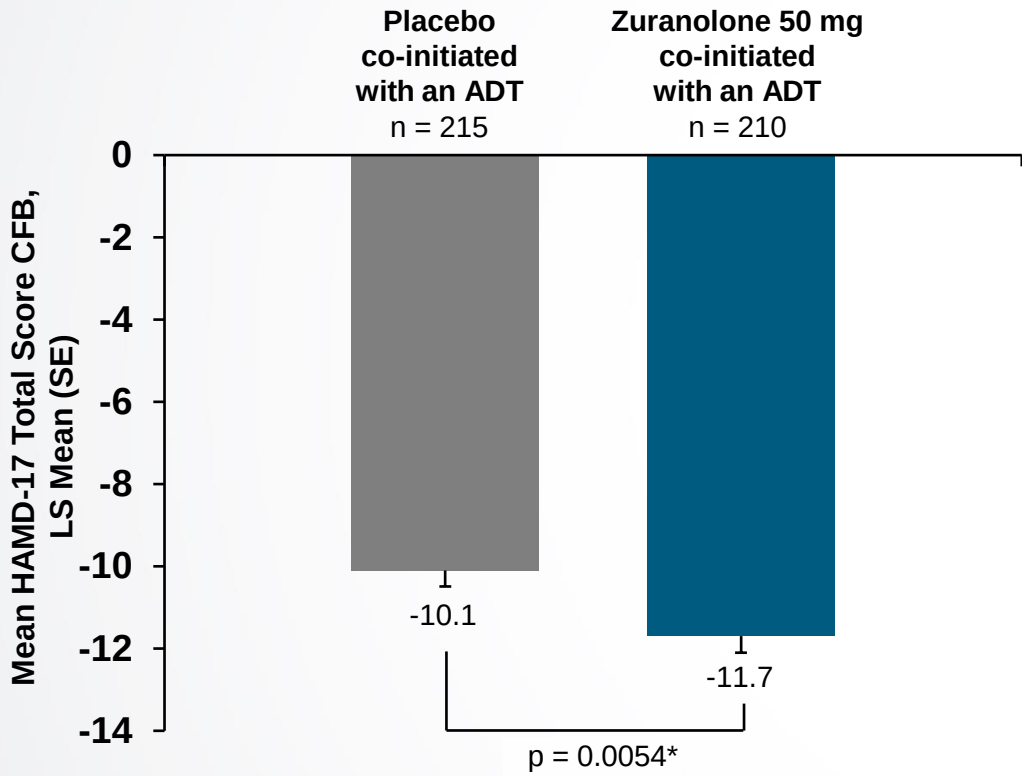
CORAL Study: Key Secondary Endpoint Result

CORAL STUDY

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.

[†]Blinded treatment period is defined as the time from first dose to last dose of zuranolone 50 mg in a 2-week treatment course plus 1 day (Day 15). [‡]Primary endpoint.
ADT = antidepressant therapy; CFB = change from baseline; HAMD-17 = 17-item Hamilton Rating Scale for Depression; LS = least squares; SE = standard error.
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/.

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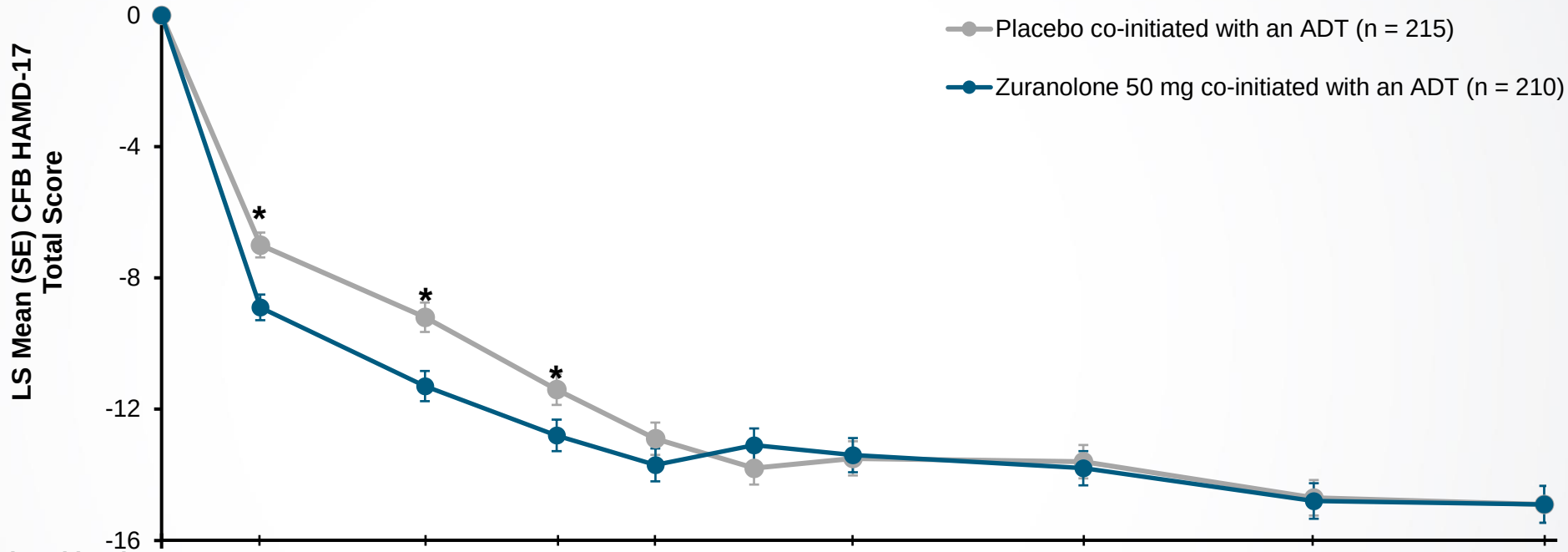
CORAL Study: CFB in HAMD-17 Total Score at Each Time Point in the Study Period by Treatment Group (FAS)



Time (days)	BL	3	8	12	15	18	21	28	35	42
Placebo co-initiated with ADT (n)		210	202	191	197	190	173	184	172	176
Zuranolone 50 mg co-initiated with ADT (n)		204	205	188	189	181	166	179	167	177
		p=0.0004	p=0.0012	p=0.0381	p=0.2477	p=0.3065	p=0.8733	p=0.6872	p=0.8918	p=0.9248
		Primary Endpoint								

***p<0.05 (all p values are nominal and not adjusted for multiplicity except for Day 3).**

ADT = antidepressant therapy; BL = baseline; CFB = change from baseline; FAS = full analysis set; HAMD-17 = 17-item Hamilton Rating Scale for Depression; LS = least squares; SE = standard error.

Data on file. Topline Results Memo; CORAL: 217-MDD-305. Feb 2022.

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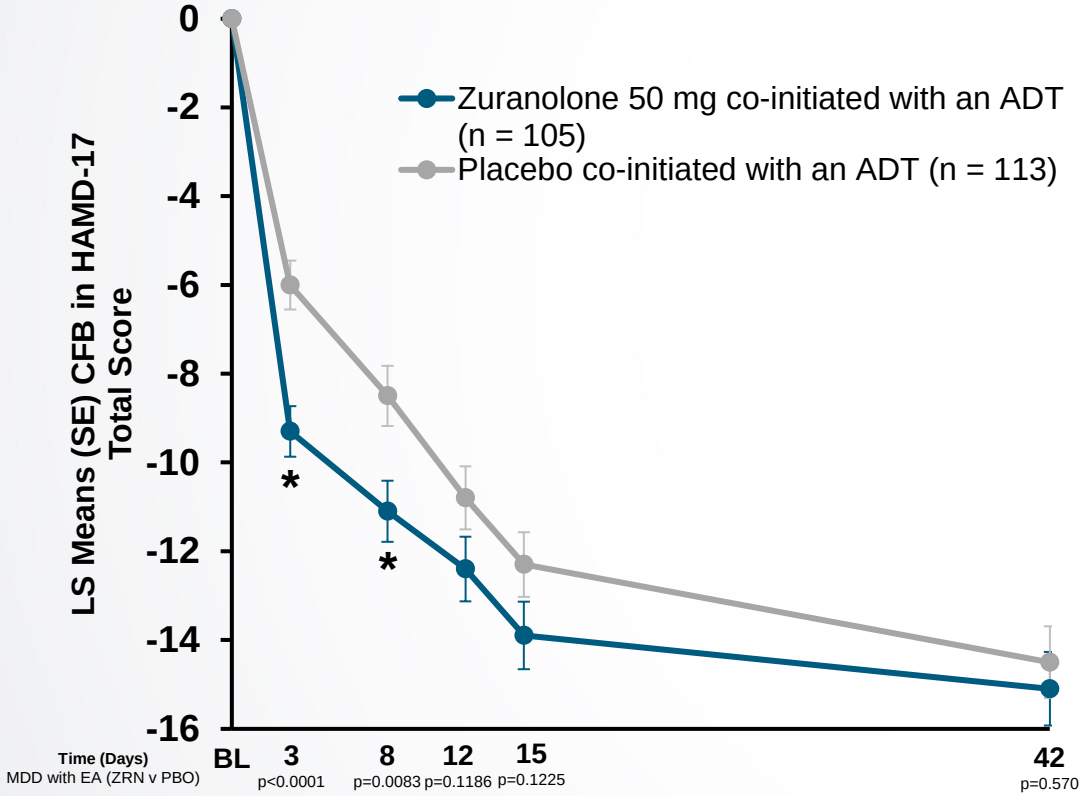
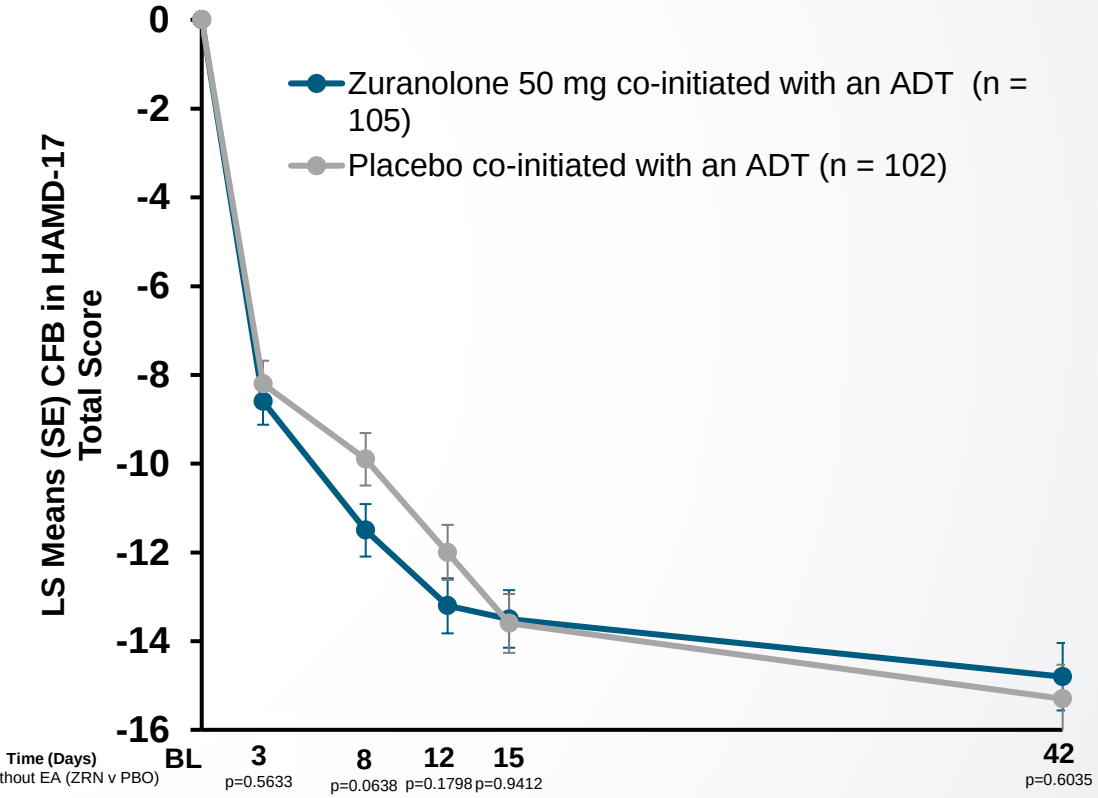
CORAL Study

LSM CFB HAMD-17 Total Score from Baseline Through Day 15
MDD with elevated anxiety as a key symptom of depression (baseline HAM-A ≥ 20)

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



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



***p<0.05 (all p values are nominal and not adjusted for multiplicity).**

ADT = antidepressant therapy; BL = baseline; CFB = change from baseline; HAMD-17 = 17-item Hamilton Rating Scale for Depression; LS = least squares; SE = standard error.

Data on file. Topline Results Memo; CORAL: 217-MDD-305. Feb 2022.

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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 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[1,2]

	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/.

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Summary and Conclusions

- The CORAL Study (217-MDD-305) was a Phase 3, randomized, double-blind, placebo-controlled trial comparing the efficacy and safety of zuranolone 50 mg co-initiated with an ADT vs placebo co-initiated with an ADT in adults with MDD.[1,2]
- The CORAL study met its primary endpoint, with zuranolone 50 mg co-initiated with an ADT demonstrating a statistically significant improvement in depressive symptoms as measured by change from baseline in HAMD-17 total score at Day 3 compared to placebo co-initiated with an ADT.[2,3]
- The key secondary endpoint was met; a statistically significant improvement in depressive symptoms was observed over the blinded treatment period* for patients treated with zuranolone 50 mg co-initiated with an ADT compared to patients treated with placebo co-initiated with an ADT.[2,3]
- In the CORAL Study, zuranolone 50 mg co-initiated with an ADT was generally well-tolerated with no new safety signals identified.[2,3]
  - The majority of patients in both treatment arms reported TEAEs that were mild or moderate in severity.
  - Over the study period, the AEs that were ≥10% in either arm were somnolence, dizziness, headache, and nausea.
  - No signals for suicidal ideation/behavior or withdrawal symptoms were identified.

*Blinded Treatment period = time from first dose to last dose of zuranolone 50 mg or placebo co-initiated with an ADT in a 2-week treatment course plus 1 day (Day 15); assessed using equal weights for Days 3, 8, 12, and 15.
ADT = antidepressant therapy; AE = adverse event; HAMD-17 = 17-item Hamilton Rating Scale for Depression; MDD = major depressive disorder.
1. CORAL. ClinicalTrials.gov Identifier: NCT04476030. 2. CORAL Press Release. Feb 2022. https://investor.sagerx.com/press-releases/. 3. Data on file. Topline Results Memo; CORAL: 217-MDD-305. Feb 2022.

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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

Q&A