217-MDD-301B WATERFALL Topline Data

June 15, 2021

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 planned timing for reporting of data from ongoing clinical trials; the potential profile and benefit of zuranolone in MDD and PPD; the potential for future regulatory filing and approval of zuranolone; plans for discussions of next steps with the FDA; regulatory filing plans and potential pathways and opportunities for zuranolone; planned next steps for the program; our estimates as to the number of patients with MDD and PPD; the target profile and potential for zuranolone; the goals and plans for our product candidates and for our research activities; the mission, vision, goals and potential for our business. 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 ongoing and future clinical trials for zuranolone or any of our other product candidates may not meet their primary endpoints or key secondary endpoints. Success in prior clinical trials may not be repeated or observed in ongoing, planned or future studies or in the same or different indications. Non-clinical and clinical results from ongoing or future trials may not support filing for regulatory approval or our ability to achieve regulatory approval on the timelines we expect or at all or may impact future development or we may be required to conduct, or decide we need, additional clinical trials or nonclinical studies.
- Unexpected concerns may arise from additional data, analysis or results from any of our completed studies.
- We may experience slower than expected enrollment in our clinical trials or may encounter other delays or problems, including in analyzing data or requiring the need for additional analysis, data or patients, and such issues with any trial could cause delay in completion of the trial, availability of results and timing of future activities.
- We may encounter unexpected safety or tolerability issues with respect to zuranolone or our other product candidates or identify other issues in clinical trials;
- At any stage, regulatory authorities may ask for additional clinical trials, nonclinical studies or other data in order for us to proceed further in development or to file for or obtain regulatory approval. The FDA and other regulatory authorities may ultimately decide that the design or results of our completed, ongoing or planned clinical trials 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. 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 not be successful in our development of any of our product candidates in any indication we are currently pursuing or may in the future pursue;
- Even if our products are successfully developed and approved, the number of patients with the MDD, PPD or the other diseases or disorders for which we are developing zuranolone and our other product candidates, and the actual market for such product candidates, if approved, may be smaller than our current estimates; or we may not achieve market acceptance or reimbursement at acceptable levels.
- Our efforts 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 generate sufficient data to file an IND on one or more earlier stage compounds at the rates we expect or at all.
- We may not be able to obtain and maintain adequate intellectual property protection or other forms of data and marketing exclusivity, 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 zuranolone or our other product candidates are being developed.
- We may not be able to establish and maintain key business relationships with third parties on 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.

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Sage is a leader in brain health – *making medicines that matter*

- Advancing brain health leadership
- Mission to be a top-tier biopharmaceutical company in the next 5 years
- Rich pipeline across 3 franchises
  - First and only product approved specifically for postpartum depression
  - Three late-stage programs; four ongoing phase 3 studies
  - 5 NCE development programs across 12+ indications
  - Strong intellectual property strategy
- Goal of 2 or more IND-enabling programs per year by 2023
- Catalyst rich 2021; topline readouts from three programs to date; six additional readouts expected
- $2B+ capital to fund efforts to accelerate and advance medicines that have potential to impact an estimated > 450M patients globally

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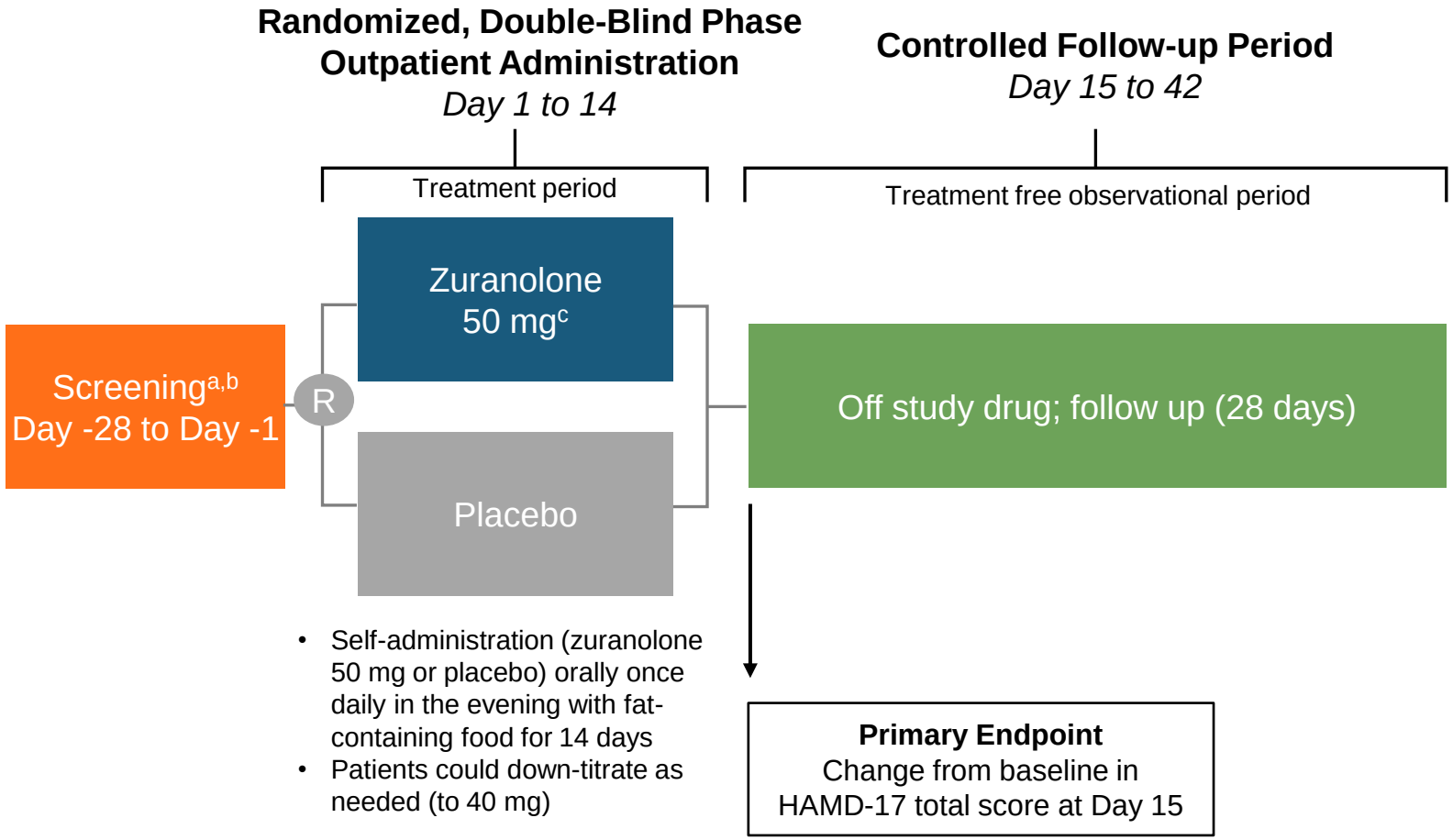
WATERFALL Study Design



[a]Day -28 to Day -1 refer to timing relative to first day of dosing with zuranolone. [b]Eligible subjects will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn ≥60 days).
[c] HAMD-17 = 17-item Hamilton Rating Scale for Depression.
Sage Therapeutics, Inc. Data on file. Protocol Number 217-MDD-301 B. September 2020.

Key Inclusion/Exclusion Criteria

WATERFALL STUDY

Key Inclusion Criteria

- ✓ Female and male patients
- ✓ Aged 18-64 years
- ✓ Diagnosis of MDD by SCID-5-CT with symptoms present for ≥4 weeks
- ✓ HAMD-17 total score ≥24 at screening and Day 1 (prior to dosing)
- ✓ Patients taking antidepressants must have been taking these medications at the same dose for ≥60 days prior to Day 1 with intent to continue through the follow-up period (Day 42)

Key Exclusion Criteria

- – Active psychosis
- – Attempted suicide or at risk of suicide associated with the current episode of MDD
- – Onset of current depressive episode during pregnancy or 4 weeks postpartum, or the patient has presented for screening during the 6-month postpartum period
- – Medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder
- – Treatment-resistant depression, defined as persistent depressive symptoms despite treatment with adequate doses of antidepressants within the current MDE (excluding antipsychotics) from 2 different classes for ≥4 weeks of treatment

'Day 1' refers to timing relative to first day of dosing with zuranolone.
HAMD-17 = 17-item Hamilton Rating Scale for Depression; MDD = major depressive disorder; MDE = major depressive episode; SCID-5-CT = Structured Clinical Interview for DSM-5 Clinical Trials Version.

Sage Therapeutics, Inc. Data on file. Protocol Number 217-MDD-301 B. September 2020.

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WATERFALL Endpoints

WATERFALL STUDY

Primary Endpoint

- *Day 15*: Change from baseline (CFB) in the 17-item Hamilton Rating Scale for Depression (HAMD-17) total score

Key Secondary Endpoints

- *Day 15:* CFB in CGI-S
- CFB in HAMD-17 total score at:
  - *Day 8*
  - *Day 3*
  - *Day 42*

Key secondary endpoints tested sequentially with a significance level of 0.05 at each step (formal testing stopped if the p-value at any step was >0.05)

Other Secondary Endpoints

- *Day 15, Day 42:* HAMD-17 response (≥ 50% reduction in HAMD-17 total score since baseline) and remission (HAMD-17≤7)
- *Day 15*: CFB in MADRS total score
- *Day 15*: CGI-I response ("much" or "very much" improved)
- *Day 15*: CFB in HAM-A total score
- *Day 15*: CFB in patient-rated SF-36v2, PHQ-9

Safety

- Incidence, severity of adverse events/serious adverse events
- Suicidal ideation and behavior (C-SSRS)
- Laboratories, electrocardiogram, vital signs, PWC-20

'Day 3', 'Day 15', 'Day 28', and 'Day 42' refer to timing relative to first day of dosing with zuranolone.
P values pertaining to the other secondary endpoints are nominal.
CGI-I = Clinical Global Impression scale – Improvement;
CGI-S = Clinical Global Impression scale – Severity;
C-SSRS = Columbia Suicide Severity Rating Scale;
HAM-A = Hamilton Rating Scale for Anxiety;
MADRS = Montgomery-Åsberg Depression Rating Scale;
PWC-20 = 20-item Physician's Withdrawal Checklist.

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Sage Therapeutics, Inc. Data on file. Protocol Number 217-MDD-301 B. September 2020.

WATERFALL Study
Disposition and Subject Progression

	Zuranolone 50 mg (n = 271)	Placebo (n = 272)
Dosed	268	269
Completed study – n (%)	242 (90.3)	235 (87.4)
Discontinued study – n (%)	26 (9.7)	34 (12.6)
Reasons for discontinuation		
Adverse events – n (%)	6 (2.2)	2 (0.7)
Withdrawal by patient – n (%)	10 (3.7)	18 (6.7)
Lost to Follow-up – n (%)	7 (2.6)	7 (2.6)
Non-compliance study drug – n (%)	1 (0.4)	3 (1.1)
Physician decision – n (%)	1 (0.4)	2 (0.7)
Other – n (%)	1 (0.4)	2 (0.7)

Percentages are based on number of subjects dosed. Sage Therapeutics, Inc. Data on file. 217-MDD-301 B topline memo. Data on file.

WATERFALL Study Demographics

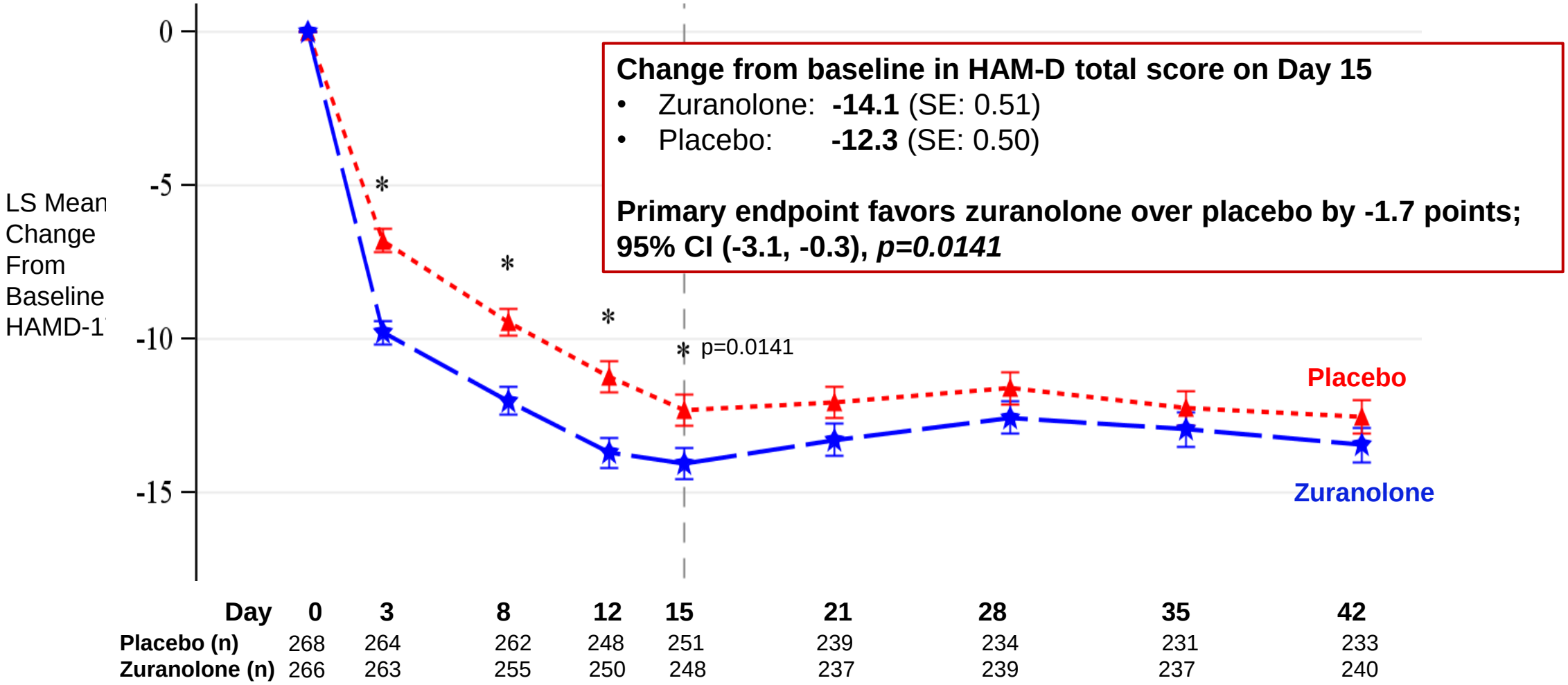
	Zuranolone 50 mg (n = 268)	Placebo (n = 269)
Age – mean, years (SD)	39.4 (12.3)	40.1 (12.6)
Female sex – n (%)	186 (69.4)	166 (61.7)
Race / Ethnicity – n (%)		
White	169 (63.1)	206 (76.6)
Black/African American	75 (28.0)	46 (17.1)
Other	24 (9.0)	17 (6.3)
Ethnicity Hispanic/Latino	58 (21.6)	54 (20.1)
BMI – mean, kg/m^2 (SD)	29.6 (6.3)	30.3 (6.2)
HAMD-17 total score at baseline – mean (SD)	26.8 (2.6)	26.9 (2.7)
Use of antidepressants at baseline – n (%)	79 (29.5)	81 (30.1)

Sage Therapeutics, Inc. Data on file. 217-MDD-301 B topline memo. Data on file.

WATERFALL Study

Primary Endpoint

HAMD-17 Total Score LS Mean Change From Baseline at Day 15 (and other timepoints)



Change from baseline in HAM-D total score on Day 15

- Zuranolone: **-14.1** (SE: 0.51)
- Placebo: **-12.3** (SE: 0.50)

Primary endpoint favors zuranolone over placebo by -1.7 points; 95% CI (-3.1, -0.3), *p=0.0141*

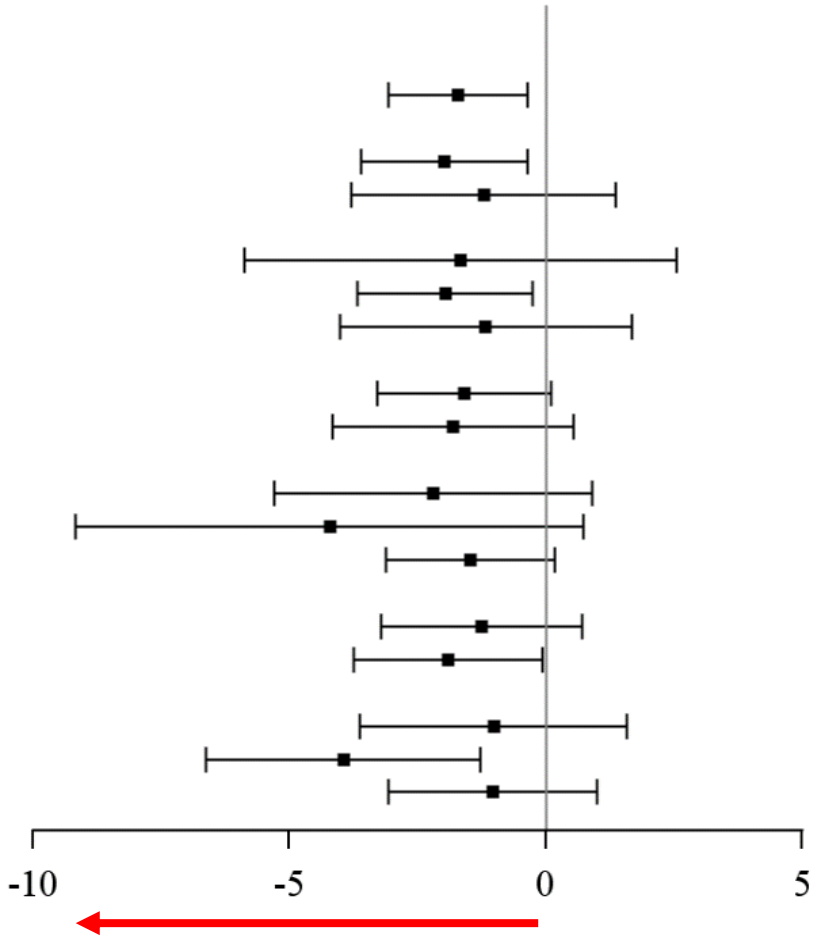
Day	0	3	8	12	15	21	28	35	42
Placebo (n)	268	264	262	248	251	239	234	231	233
Zuranolone (n)	266	263	255	250	248	237	239	237	240

LS = least squares.

Sage Therapeutics, Inc. Data on file. 217-MDD-301 B topline memo.

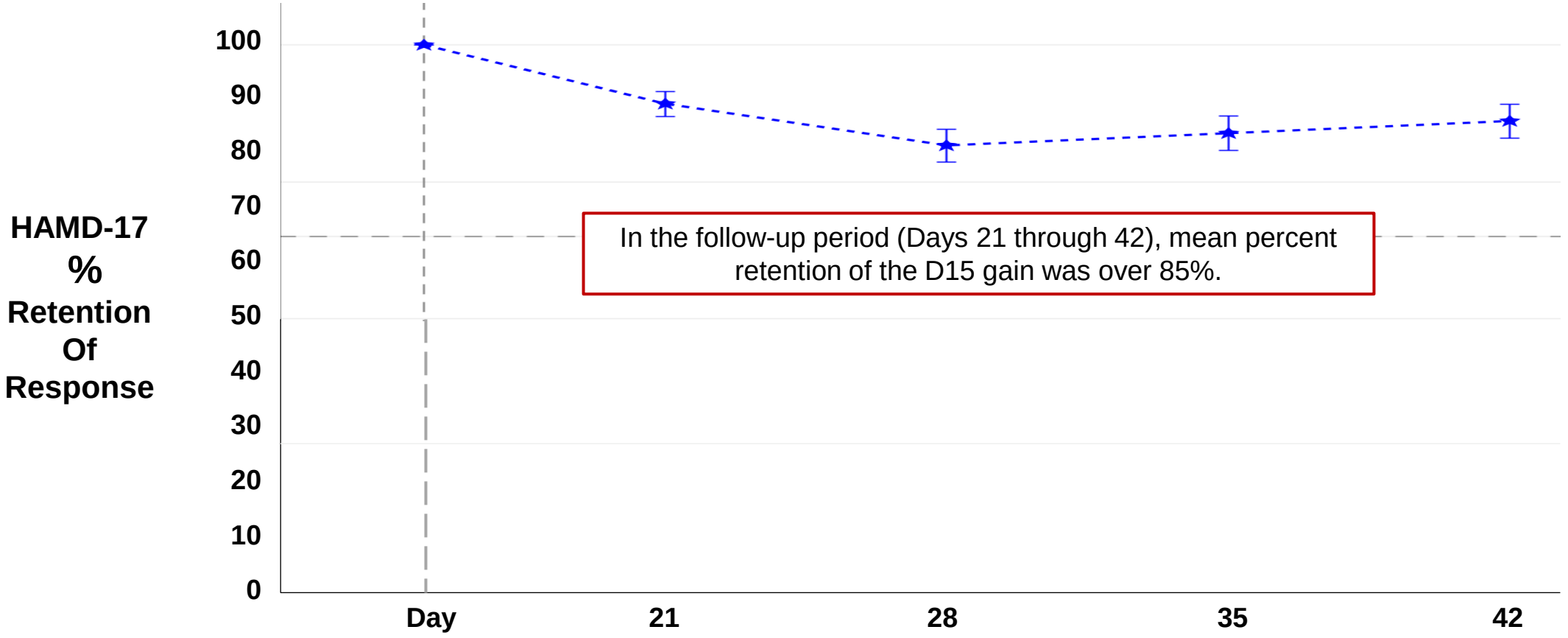
WATERFALL Study
HAMD-17 Subgroups: Day 15

Subgroups	Count	LS Mean Diff	Low	High	P-value
HAM-D Total Score					
Overall	499	-1.71	-3.08	-0.35	0.0141
Antidepressant use at Baseline					
No	347	-1.98	-3.60	-0.36	0.0165
Yes	152	-1.21	-3.79	1.37	0.3552
Age Group					
18-24 years	58	-1.67	-5.89	2.55	0.4305
25-50 years	308	-1.96	-3.67	-0.25	0.0248
51-64 years	133	-1.18	-4.02	1.67	0.4145
Sex					
Female	329	-1.58	-3.28	0.11	0.0671
Male	170	-1.81	-4.17	0.55	0.1326
Race Group					
Black or African American	103	-2.20	-5.30	0.90	0.1632
Other	38	-4.22	-9.18	0.73	0.0924
White	358	-1.47	-3.12	0.17	0.0793
Baseline HAM-D Total Score					
<26	192	-1.25	-3.22	0.71	0.2106
>=26	307	-1.91	-3.75	-0.06	0.0433
BMI (kg/m2) at Baseline Group					
18.5-24.9 kg/m2	117	-1.02	-3.63	1.58	0.4393
25-29.9 kg/m2	130	-3.94	-6.62	-1.27	0.0041
>= 30 kg/m2	247	-1.04	-3.06	0.99	0.3157



WATERFALL Study

Mean (SE) of % Day 15 CFB retained at subsequent visits
*(Full Analysis Set; Day 15 zuranolone responders only)**

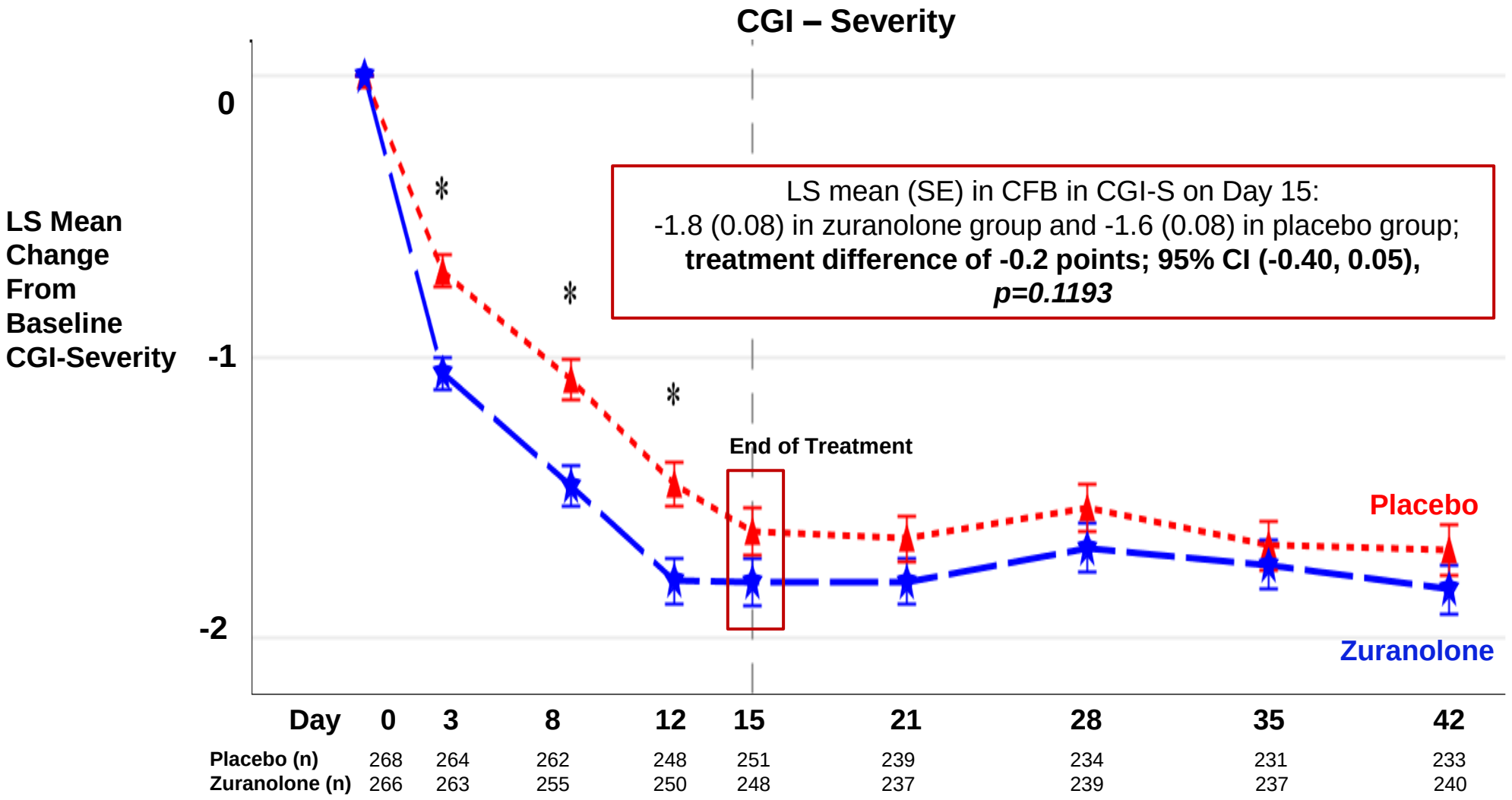


*Percent retention of Day 15 HAMD-17 total score reduction from baseline is the change from baseline in HAMD-17 total score at post-Day 15 visits as percentage of change from baseline at Day 15 and was evaluated in Day 15 HAMD-17 responders only in the zuranolone treatment group (≥50% change in HAMD-17 total score at Day 15 versus baseline).

Sage Therapeutics, Inc. Data on file. 217-MDD-301 topline memo.

WATERFALL Study

Clinical Global Impression-Severity of Illness (CGI-S) - First Key Secondary endpoint

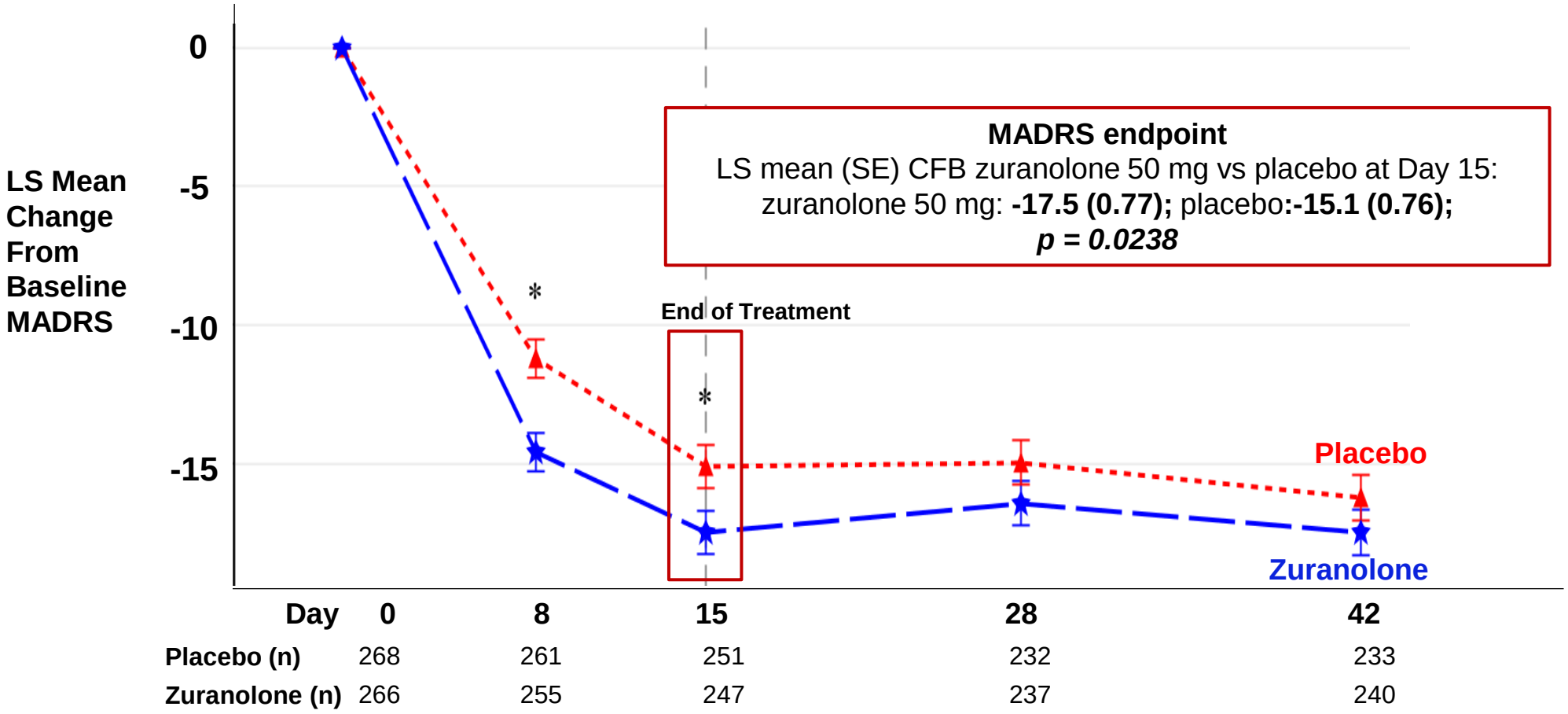


CGI-S Scale	
Normal, not at all ill	1
Borderline ill	2
Mildly ill	3
Moderately ill	4
Markedly ill	5
Severely ill	6
Among the most extremely ill	7

Sage Therapeutics, Inc. Data on file. 217-MDD-301B topline memo.

WATERFALL Study

Change From Baseline in MADRS Total Score at Day 15



NOTE: P values pertaining to other secondary endpoints are nominal; CFB = change from baseline; *p < 0.05

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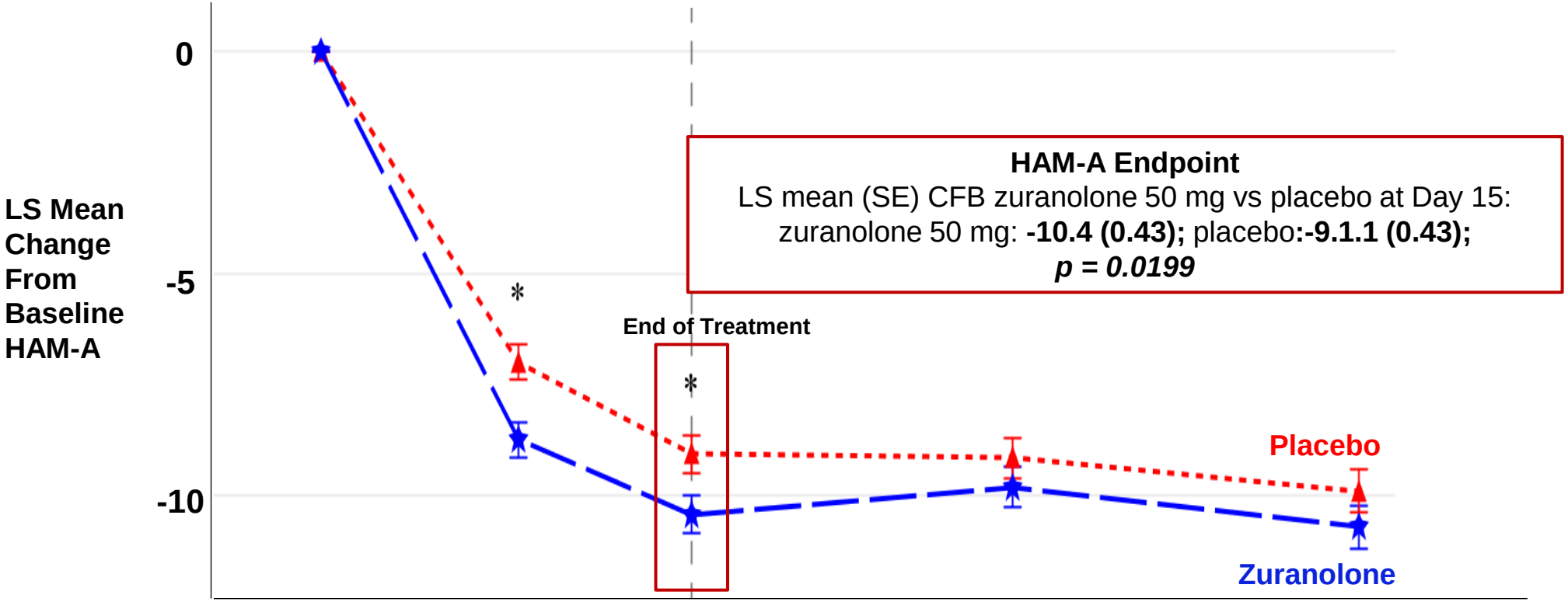
WATERFALL Study

Change From Baseline in HAM-A Total Score at Day 15

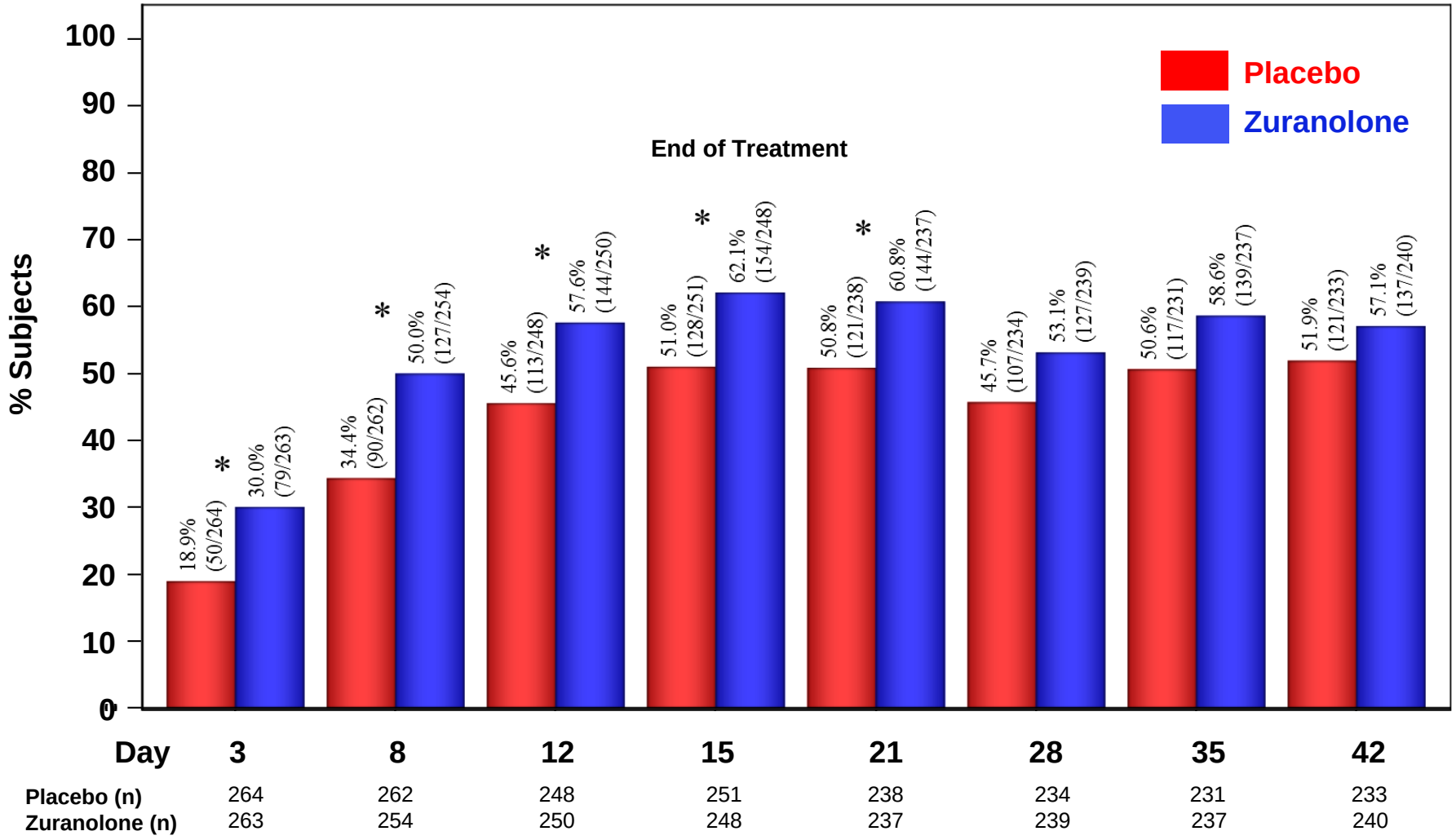


NOTE: P values pertaining to other secondary endpoints are nominal; CFB = change from baseline; *p < 0.05

Sage Therapeutics, Inc. Data on file. 217-MDD-301B topline memo.

WATERFALL Study
CGI-Improvement Response

CGI – Improvement Response
('Much' or 'Very Much' Improved)



* =p <0.05 for odds ratio. Sage Therapeutics, Inc. Data on file. 217-MDD-301 B topline memo.

WATERFALL Study
Primary and select secondary statistical outcomes

Outcome	Day 3	Day 8	Day 12	Day 15
HAM-D-17: LS mean TRT diff (p value)	-3.0 (<0.0001)^	-2.6 (<0.0001)^	-2.5 (0.0003)	-1.7 (0.014)*
CGI-Severity: LS mean TRT diff (p value)	-0.4 (<0.0001)	-0.4 (0.0001)	-0.3 (0.0014)	-0.2 (0.1193)^
CGI-Improvement Response: Odds ratio (p value)	1.8 (0.0032)	1.9 (0.0005)	1.6 (0.010)	1.5 (0.0191)
MADRS: LS mean TRT diff (p value)	Not measured per protocol	-3.4 (0.0003)	Not measured per protocol	-2.4 (0.024)
HAM-A: LS mean TRT diff (p value)	Not measured per protocol	-1.7 (0.0011)	Not measured per protocol	-1.4 (0.0199)

Except for HAMD-17 at Day 15 (primary) which was statistically significant and CGI-S (first secondary endpoint) which was not significant at Day 15, all p-values in the table are nominal and not adjusted for multiple comparisons.
*Pre-specified primary endpoint
^Pre-specified key secondary endpoints
LS = least squares; LS mean difference = difference in LS means of change from baseline between zuranolone and placebo groups

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Sage Therapeutics, Inc. Data on file. 217-MDD-301 B topline memo.
Data on file.

WATERFALL Study Safety

- TEAEs consistent with known zuranolone profile,[1,2] with ~60% patients receiving zuranolone 50 mg and ~45% receiving placebo reporting ≥1 TEAE.
- Most TEAEs reported by zuranolone 50 mg patients were mild or moderate in severity.
- 2 zuranolone 50 mg patients and 2 placebo patients experienced serious adverse events (SAEs); none related to sedation.
- No deaths, no loss of consciousness, weight gain, sexual dysfunction, or euphoria reported.
- Most common TEAEs leading to study drug (zuranolone) discontinuation were dizziness and sedation.

Overview of TEAEs through Day 42

Patients with TEAEs	Zuranolone 50 mg (n = 268)	Placebo (n = 269)
At least 1 TEAE – n (%)	161 (60.1)	120 (44.6)
Mild – n (%)	86 (32.1)	76 (28.3)
Moderate – n (%)	67 (25.0)	41 (15.2)
Severe – n (%)	8 (3.0)	3 (1.1)
SAE – n (%)	2 (0.7)	2 (0.7)
Dose reduction due to TEAE – n (%)	23 (8.6)	1 (0.4)
Discontinuation of treatment due to TEAEs – n (%)	9 (3.4)	4 (1.5)
Discontinuation of study due to TEAEs – n (%)	5 (1.9)	2 (0.7)
Death – n (%)	0	0

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WATERFALL Study Safety

- The most common (>5%) events were somnolence, dizziness, headache, and sedation in patients receiving zuranolone 50 mg and diarrhea and headache in patients receiving placebo.
- The most common TEAEs observed on zuranolone 50 mg are consistent with the safety profile of zuranolone known to date.*

All TEAEs (>5%) incidence through Day 42

Preferred Terms (PTs)	Zuranolone 50 mg (n = 268)	Placebo (n = 269)
Somnolence	41 (15.3%)	8 (3.0%)
Dizziness	37 (13.8%)	6 (2.2%)
Headache	29 (10.8%)	21 (7.8%)
Sedation	20 (7.5%)	1 (0.4%)
Diarrhea	8 (3.0%)	14 (5.2%)

Sage Therapeutics, Inc. Data on file. 217-MDD-301B topline memo. *Gunduz-Bruce H et al. *N Eng J Med*. 2019;381(10):903-911

WATERFALL Study
Safety

Additional safety findings

- **Suicidality**: No signal of increased suicidal ideation/behavior as assessed by the C-SSRS was observed throughout the study in patients receiving zuranolone 50 mg or patients receiving placebo.
- **Withdrawal symptoms:** No signals for withdrawal symptoms assessed by the PWC-20 at Day 18 or 21; scores were similar after discontinuation of zuranolone 50 mg or placebo

  Change from first PWC-20 assessment (SD) at Day 18; zuranolone vs placebo: -1.2 (4.3) vs -1.2 (4.3);
  Day 21; zuranolone vs placebo -0.3 (4.6) vs -0.5 (4.4)

- **Concomitant antidepressant therapy (ADT):** No clinically meaningful differences in the safety profile for zuranolone 50 mg monotherapy compared with those receiving zuranolone 50 mg in combination with pre-existing ADT.

PWC-20 = 20-item Physician Withdrawal Checklist.
Sage Therapeutics, Inc. Data on file. 217-MDD-301B topline memo.

Key takeaways
Benefit/risk

- The WATERFALL study met its primary endpoint at Day 15, with statistically significant reduction in HAM-D total score on Day 15
  - LS mean (SE) CFB in HAM-D total score on Day 15 -14.1 (0.51) (zuranolone) vs. -12.3 (0.50) (placebo); Δ ***-1.7 points**; **95% CI (-3.1, -0.3), p=0.0141***
  - Early effect was evident with significant differences in HAM-D noted at Days 3, 8, and 12
  - Patients with a response at Day 15 in the zuranolone group retained 86.1% of their HAMD-17 improvement at Day 42 (4 weeks after dosing ended).
- The pre-specified analysis model of first key secondary endpoint - CGI-S at Day 15 - was not statistically significant
- Evidence of treatment effect on depressive symptoms was present in favor of zuranolone across all levels of subgroups
- Zuranolone 50 mg was generally well tolerated
  - Discontinuation of IP due to TEAEs were 3.4% and 1.5% in the zuranolone and placebo groups, respectively.
  - Dose reductions in IP were 8.6% and 0.4% in the zuranolone and placebo groups, respectively.
- Zuranolone was well tolerated; adverse events were consistent with the safety profile seen to date

Q&A

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