Rapid Improvements in MADRS With Zuranolone in Major Depressive Disorder And Postpartum Depression: Results From the LANDSCAPE/NEST Clinical Development Programmes

Anita H. Clayton, MD[1]; Kristina M. Deligiannidis, MD[2]; J. Antoni Ramos-Quiroga, MD, PhD[3]; Robert Lasser, MD, MBA[4]; Abdul J. Sankoh, PhD[4]; Bridgette Leclair, PharmD[5]; Mona Kotecha, MD[5]; James Doherty, PhD[4]

31st European Congress of Psychiatry
27 March 2023, Paris, France

[1]Department of Psychiatry and Neurobehavioral Sciences, University of Virginia School of Medicine, Charlottesville, VA, USA; [2]Department of Psychiatry, Zucker Hillside Hospital, Glen Oaks, NY, USA, and Feinstein Institutes for Medical Research, Northwell Health, Manhasset, NY, USA; [3]Department of Psychiatry, Hospital Universitari Vall d'Hebron, Barcelona, Spain; [4]Sage Therapeutics, Inc., Cambridge, MA, USA; [5]Biogen Inc., Cambridge, MA, USA

MRC-217-01184 03/23

Disclosures

- **Anita H. Clayton, MD,** reports grants from Daré Bioscience, Janssen, Otsuka, Praxis Precision Medicines, Relmada Therapeutics, Inc., and Sage Therapeutics, Inc.; consulting fees from AbbVie, Inc., Brii Biosciences, Inc., Fabre-Kramer, Janssen Research & Development, LLC, Mind Cure Health, Ovoca Bio plc, Praxis Precision Medicines, PureTech Health, Reunion Neuroscience (formerly Field Trip Health) S1 Biopharma, Sage Therapeutics, Inc., Takeda/Lundbeck, Vella Bioscience, Inc., and WCG MedAvante-ProPhase; royalties from Ballantine Books/Random House, the Changes in Sexual Functioning Questionnaire, and Guilford Publications; and restricted stock in Euthymics, Mediflix LLC, and S1 Biopharma.

- **Kristina M. Deligiannidis, MD,** serves as a consultant to Sage Therapeutics, Inc., Brii Biosciences, Inc., and GH Research Ireland Limited, and reports grants awarded to Zucker Hillside Hospital/Feinstein Institutes for Medical Research during the conduct of the brexanolone injection and zuranolone clinical trials. Dr. Deligiannidis also received grants from NIH and Vorso Corporation and royalties from an NIH employee invention outside of the submitted work.

- **J. Antoni Ramos-Quiroga, MD, PhD,** was on the speakers bureau and/or served as consultant for Janssen-Cilag, Novartis, Shire, Takeda, BIAL, Shionogi, Sincrolab, Novartis, BMS, Medice, Technofarma, Rubió, and Raffo in the last 3 years. He also received travel awards (air tickets and hotel) for taking part in psychiatric meetings from Janssen-Cilag, Rubió, Shire, Takeda, Shionogi, BIAL, and Medice. The Department of Mental Health chaired by him received unrestricted educational and research support from the following companies in the last 3 years: Janssen-Cilag, Shire, Oryzon, Roche, Psious, and Rubió.

- **Robert Lasser, MD, MBA; Abdul J. Sankoh, PhD;** and **James Doherty, PhD,** are employees of Sage Therapeutics, Inc., and may hold stock and/or stock options.

- **Bridgette Leclair, PharmD,** and **Mona Kotecha, MD,** are employees of Biogen Inc. and may hold stock.

MRC-217-01184 03/23

Background

- Depression may result from imbalanced signalling pathways, including dysfunctional GABA signalling in the brain.[1-3]
- Despite currently available treatments, many people living with depression experience symptoms that can be debilitating and lead to functional impairment.[4-6] Most ADTs typically require a 6- to 8-week period to determine efficacy.[7,8]
- There is need for ADTs that can offer a rapid onset of action without requiring chronic use[7] in both MDD and PPD. There are currently no approved ADTs for treating patients with PPD in the EU.
- Zuranolone is an investigational, oral, positive allosteric modulator of synaptic and extrasynaptic $GABA_A$ receptors and neuroactive steroid in clinical development as a once-daily, 14-day treatment course for adults with MDD and PPD.
  - Adults who received zuranolone (30 mg or 50 mg) demonstrated greater improvement in depressive symptoms, as measured by significantly greater change from baseline in HAMD-17 total score at Day 15 than participants who received placebo in 4 out of 5 completed studies, with improvements observed as early as Day 2 or 3 [9-13,a]

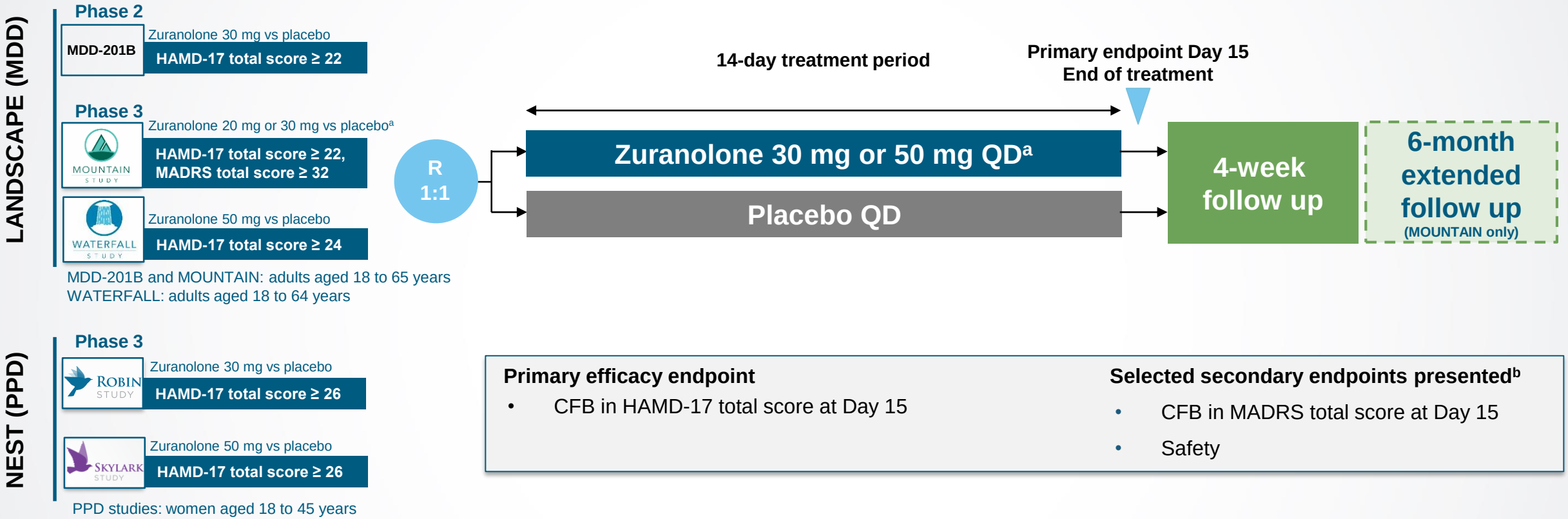
MRC-217-01184 03/23

Objective

- The objective of this presentation is to evaluate the efficacy (assessed by the Montgomery–Åsberg Depression Rating Scale [MADRS]) and safety of zuranolone versus placebo across 5 clinical studies in MDD and PPD.
  - Both HAMD-17 and MADRS are widely used scales to assess the symptoms of depression.[1]
  - The CFB in MADRS total score was a secondary endpoint in the zuranolone clinical studies.[2-6,a]
  - The HAMD-17 has greater weight for somatic symptoms of depression (e.g., sleep, anxiety), and the MADRS has a greater weight for mood symptoms of depression (e.g., sadness, pessimistic thoughts).[1,7]

MRC-217-01184 03/23

Study design



Primary efficacy endpoint

- CFB in HAMD-17 total score at Day 15

Selected secondary endpoints presented[b]

- CFB in MADRS total score at Day 15
- Safety

- Patients received either zuranolone or placebo once daily orally for 14 days and were followed up for at least an additional 4 weeks.
- Studies varied primarily in inclusion criteria (minimum HAMD-17 and MADRS total scores at baseline) and treatment doses of zuranolone (20 mg, 30 mg, or 50 mg).[a]

Studies included 3 MDD studies (MDD-201B, NCT03000530; MOUNTAIN, NCT03672175; WATERFALL, NCT04442490) and 2 PPD studies (ROBIN, NCT02978326; SKYLARK, NCT04442503).
CFB = change from baseline; HAMD-17 = 17-item Hamilton Rating Scale for Depression; MADRS = Montgomery–Åsberg Depression Rating Scale; MDD = major depressive disorder; PPD = postpartum depression; QD = once daily.
[a] MOUNTAIN also had a zuranolone 20-mg arm; data are not covered in this presentation. [b] Additional secondary endpoints were examined and included other efficacy and safety/tolerability outcomes that are not covered in this presentation.

MRC-217-01184 03/23

Study disposition

	LANDSCAPE (MDD)						NEST (PPD)			
	MDD-201B		MOUNTAIN[a]		WATERFALL		ROBIN		SKYLARK	
	ZRN 30	PBO	ZRN 30	PBO	ZRN 50	PBO	ZRN 30	PBO	ZRN 50	PBO
Dosed, n	45	44	192	190	268	269	78	73	98	98
Completed study, n (%)	41 (91.1)	39 (88.6)	141 (73.4)	141 (74.2)	242 (90.3)	235 (87.4)	73 (93.6)	69 (94.5)	84 (85.7)	86 (87.8)
Discontinued study, n (%)	4 (8.9)	5 (11.4)	51 (26.6)	49 (25.8)	26 (9.7)	34 (12.6)	4 (5.1)	7 (9.6)	14 (14.3)	12 (12.2)
Dose reduction, n (%)	6 (13.3)	0	NA[b]	NA[b]	23 (8.6)	1 (0.4)	0	0	16 (16.3)	1 (1.0)
Reasons for discontinuation, n (%)										
Adverse events	2 (4.4)	0	4 (2.1)	5 (2.6)	6 (2.2)	2 (0.7)	1 (1.3)	0	1 (1.0)	1 (1.0)
Withdrawal by patient	1 (2.2)	2 (4.5)	29 (15.1)	25 (13.2)	10 (3.7)	18 (6.7)	3 (3.8)	2 (2.7)	4 (4.1)	3 (3.1)
Lost to follow-up	1 (2.2)	3 (6.8)	12 (6.3)	11 (5.8)	7 (2.6)	7 (2.6)	0	3 (4.1)	6 (6.1)	8 (8.2)
Noncompliance to study drug	0	0	1 (0.5)	1 (0.5)	1 (0.4)	3 (1.1)	0	2 (2.7)	NR	NR
Physician decision	0	0	2 (1.0)	4 (2.1)	1 (0.4)	2 (0.7)	0	0	2 (2.0)	0
Other	0	0	3 (1.6)	3 (1.6)	1 (0.4)	2 (0.7)	0	0	1 (1.0)	0

Across these 5 studies, 681 participants received zuranolone 30 mg or 50 mg.

Studies included 3 MDD studies (MDD-201B, NCT03000530; MOUNTAIN, NCT03672175; WATERFALL, NCT04442490) and 2 PPD studies (ROBIN, NCT02978326; SKYLARK, NCT04442503).
MDD = major depressive disorder; NA = not applicable; NR = not reported; PBO = placebo; PPD = postpartum depression; ZRN 30 = zuranolone 30 mg; ZRN 50 = zuranolone 50 mg.
[a] Data from zuranolone 20-mg arm of the MOUNTAIN trial not included in this presentation. [b] Dose reductions were not allowed in MOUNTAIN trial.

MRC-217-01184 03/23

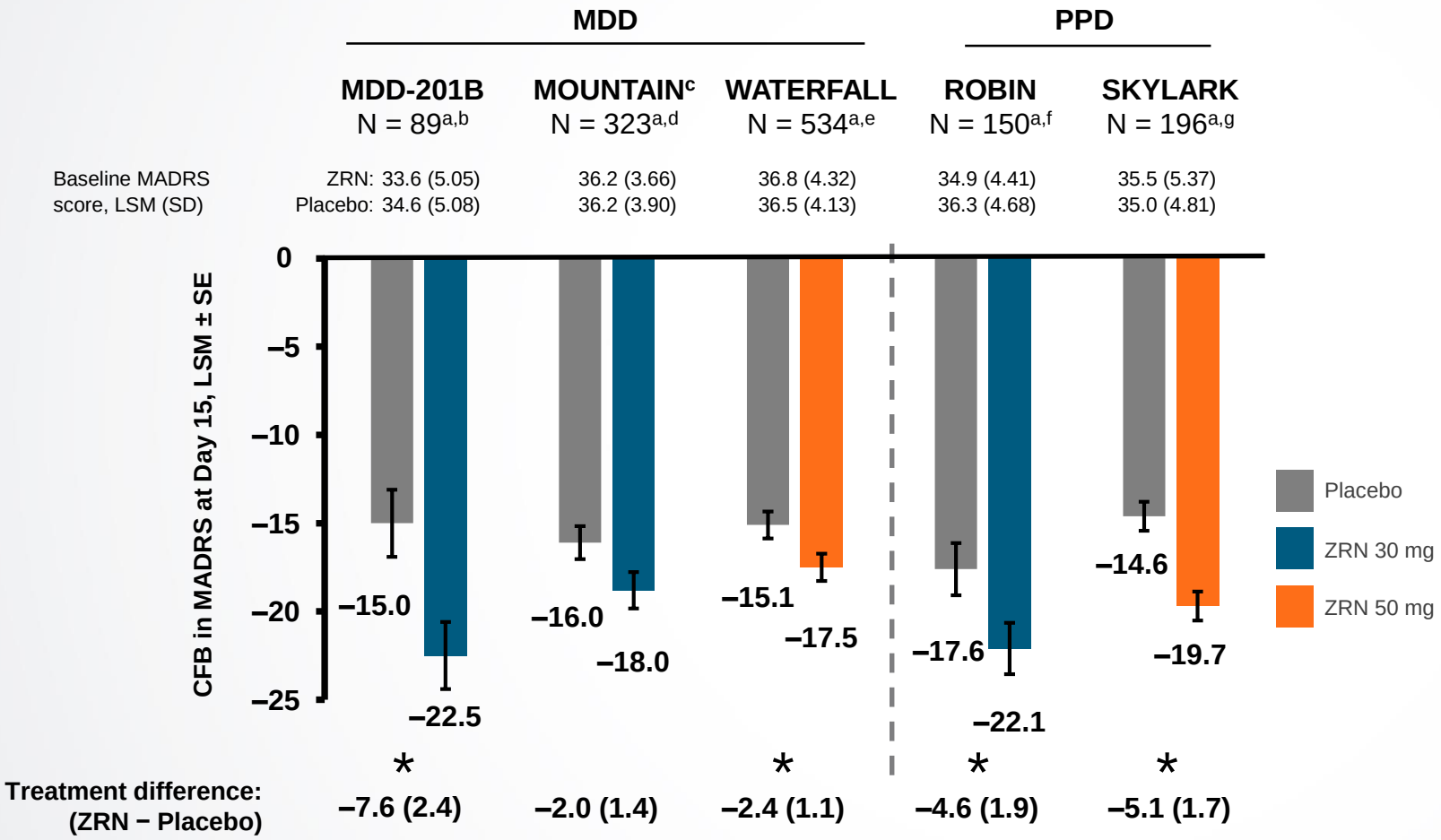
Baseline characteristics

	LANDSCAPE (MDD)						NEST (PPD)			
	MDD-201B[a]		MOUNTAIN[b]		WATERFALL[b]		ROBIN[c]		SKYLARK	
	ZRN 30	PBO	ZRN 30	PBO	ZRN 50	PBO	ZRN 30	PBO	ZRN 50	PBO
n	45	44	166	157	165	165	76	74	98	98
Age, mean (SD),years	49.1 (13.61)	38.3 (12.15)	42.3 (11.77)	41.4 (12.16)	39.7 (12.18)	40.4 (12.91)	29.3 (5.39)	27.4 (5.33)	30.0 (5.90)	31.0 (5.95)
Female, n (%)	25 (55.6)	30 (68.2)	121 (72.9)	106 (67.5)	118 (71.5)	103 (62.4)	76 (100)	74 (100)	98 (100)	98 (100)
Race, n (%)										
White	7 (15.6)	16 (36.4)	94 (56.6)	96 (61.1)	103 (62.4)	124 (75.2)	44 (57.9)	40 (54.1)	68 (69.4)	69 (70.4)
Black/African American	36 (80.0)	28 (63.6)	64 (38.6)	54 (34.4)	48 (29.1)	29 (17.6)	31 (40.8)	31 (41.9)	25 (25.5)	18 (18.4)
Other[d]	2 (4.4)	0	8 (4.8)	7 (4.4)	14 (8.4)	12 (7.2)	1 (1.3)	3 (4.2)	5 (5.1)	11 (11.2)
Ethnicity: Hispanic/Latino, n (%)	1 (2.2)	7 (15.9)	27 (16.3)	26 (16.6)	39 (23.6)	37 (22.4)	16 (21.1)	18 (24.3)	33 (33.7)	42 (42.9)
Baseline ADT use, n (%)	12 (26.7)	10 (22.7)	47 (28.3)	49 (31.2)	47 (28.5)	49 (29.7)	16 (21.1)	13 (17.6)	15 (15.3)	15 (15.3)
Baseline HAMD-17, mean (SD)	25.2 (2.58)	25.7 (2.42)	25.9 (2.88)	25.8 (3.07)	28.3 (2.26)	28.5 (2.23)	28.4 (2.09)	28.8 (2.32)	28.6 (2.49)	28.8 (2.34)
Baseline MADRS, mean (SD)	33.6 (5.05)	34.6 (5.08)	36.7 (3.49)	36.9 (3.77)	36.8 (4.32)	36.5 (4.13)	34.9 (4.41)	36.3 (4.68)	35.5 (5.37)	35.0 (4.81)

Patient populations were racially and ethnically diverse and generally balanced between treatment arms in each trial.

MRC-217-01184 03/23

Improvements in MADRS total score shown in patients who received zuranolone compared to placebo at Day 15

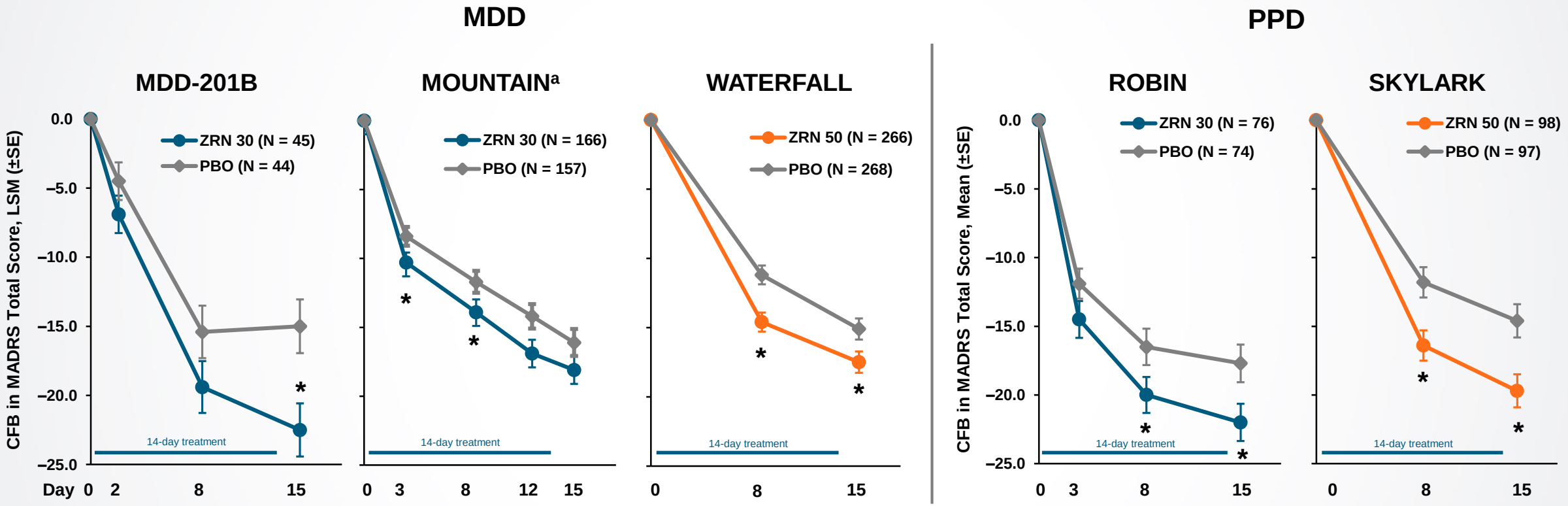


In patients with MDD or PPD who received zuranolone, nominally significant improvement in depressive symptoms at Day 15 (as assessed by CFB in MADRS total score) was shown in 4 of 5 trials vs placebo

Overall, the CFB in MADRS total score at Day 15 was consistent with the CFB in HAMD-17 in each trial (primary endpoint).

MRC-217-01184 03/23

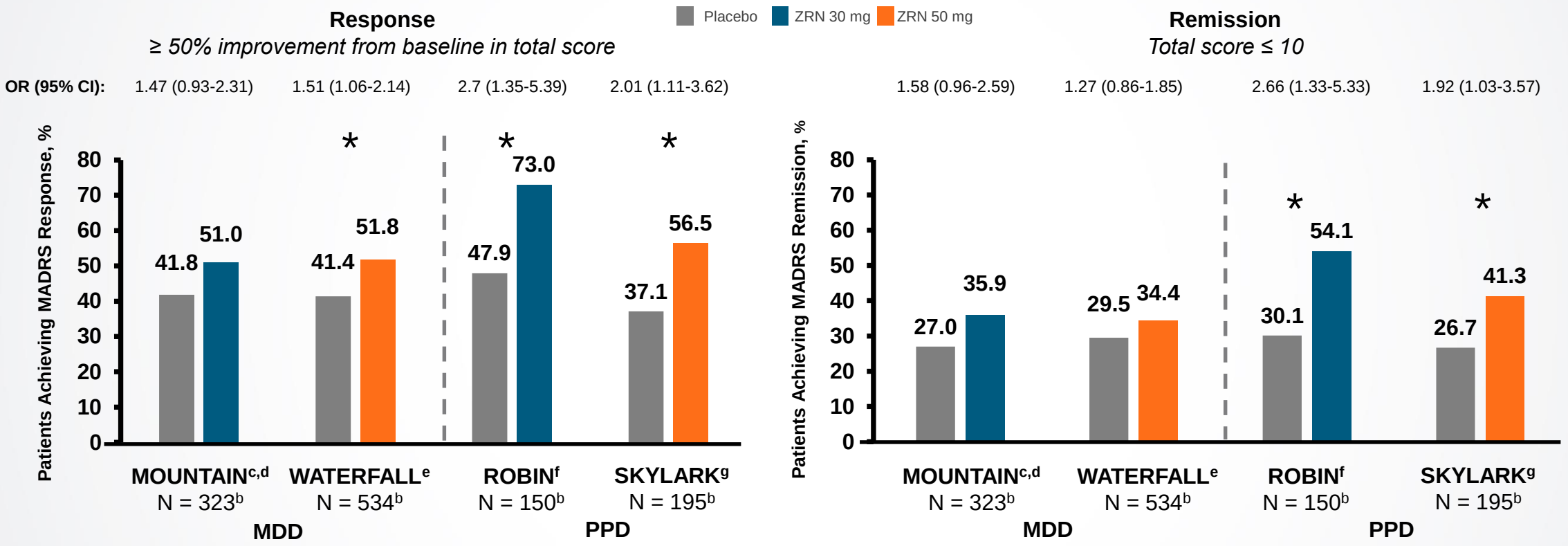
Rapid improvements in MADRS observed as early as Day 3 or Day 8



Rapid numerical improvements in MADRS total score observed as early as Day 3 or 8 in adults with MDD or PPD treated with zuranolone vs placebo.

MRC-217-01184 03/23

Response and remission rates at Day 15 were assessed using MADRS total score[a]



Patients who received zuranolone showed response rates up to 73% and remission rates up to 54%, as measured by MADRS total score at Day 15.

MRC-217-01184 03/23

Treatment with zuranolone 30 mg or 50 mg was generally well tolerated across studies

Treatment-emergent adverse events (TEAEs) with > 5% incidence in any zuranolone treatment group: safety set

Range of incidence across MDD-201B, MOUNTAIN, WATERFALL, ROBIN, and SKYLARK studies, %[a]	ZRN[a]	PBO
Somnolence	6.7–26.5	2.3–11.0
Headache	6.3–17.8	7.4–15.9
Dizziness	5.7–13.8	2.2–10.2
Sedation	4.4–11.2	0–4.5
Nausea	3.6–11.1	2.3–8.2
Upper respiratory tract infection	0–8.0	0–2.1
Diarrhoea	0–6.4	2.0–6.8
Fatigue	1.1–6.8	0–2.6

- No loss of consciousness or excessive sedation were reported as TEAEs.
- No evidence of withdrawal effects following discontinuation of zuranolone treatment was observed.[b]
- No signal for increased suicidal ideation or suicidal behavior compared with baseline was observed.[c]
- SAEs occurred in less than 3% of zuranolone-treated patients across clinical studies.

Zuranolone showed a consistent safety profile across clinical studies in adults with MDD or PPD.

MRC-217-01184 03/23

Conclusions

- In both the LANDSCAPE (MDD-201B, MOUNTAIN, and WATERFALL studies) and NEST (ROBIN and SKYLARK studies) programmes, patients with MDD or PPD receiving zuranolone showed numerical improvements in depressive symptoms as assessed by MADRS compared with placebo.
  - Nominally significant improvements in depressive symptoms at Day 15 (as assessed by MADRS total score) were observed in 4 of the 5 completed, placebo-controlled studies.
  - Numerical improvements in MADRS total score were noted as early as Day 3 or 8.
  - Numerically greater percentages of patients achieved MADRS response and remission with zuranolone compared with placebo at Day 15.
- Across studies and doses, treatment with zuranolone has been generally well tolerated, with a consistent safety profile.
- Overall, the efficacy and safety results from the LANDSCAPE and NEST clinical programmes support further development of zuranolone for potential use as a rapid-acting, 14-day treatment course for adults with MDD and PPD.

MRC-217-01184 03/23

Acknowledgements

- We would like to thank the following:
  - — the patients and their families for helping us reimagine brain health
  - — clinical investigators and their staff at sites throughout the country
- This study was sponsored by Sage Therapeutics, Inc., and Biogen Inc.
- Medical writing and editorial support was provided by MediTech Media, Ltd., and funded by Sage Therapeutics, Inc. and Biogen Inc.

Thank you

MRC-217-01184 03/23