Summary of Early (Day 2/3) and Primary (Day 15) Clinical Efficacy Outcomes from the Ongoing Clinical Development Program for Zuranolone in the Treatment of Major Depressive Disorder and Postpartum Depression

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BACKGROUND

- Treatment responses to standard-of-care (oral daily) antidepressants remain suboptimal in many patients with major depressive disorder (MDD) (e.g., extended time to response; high rate of discontinuations due to adverse events [AEs]; residual symptoms, including suicidal ideation; acute AEs; and long-term AEs associated with chronic use).[1-3]
- Thus, there is a significant unmet need for alternative, innovative treatments for depression that offer a rapid, durable effect without the need for chronic treatment.
- Dysregulated gamma-aminobutyric acid (GABA) signaling may contribute to the development of depression by disrupting adaptive signaling in key neuronal networks, such as those controlling mood, arousal, behavior, and cognition.[4-6]
- Neuroactive steroid binding to GABA type A ($GABA_A$) receptors results in potentiation of both synaptic and extrasynaptic $GABA_A$ receptors and may increase surface expression of extrasynaptic $GABA_A$ receptors. Extrasynaptic $GABA_A$ receptors containing delta subunits are insensitive to benzodiazepines.[6,7]
- Zuranolone (ZRN) is an investigational, oral neuroactive steroid and $GABA_A$ receptor positive allosteric modulator in clinical development as a once-daily, 2-week, as-needed therapy for postpartum depression (PPD) as part of the NEST program and for MDD as part of the LANDSCAPE program.[6,8]
- Here, we present a summary of efficacy data from the completed placebo-controlled trials across the NEST and LANDSCAPE programs: ROBIN, MDD-201B, and MOUNTAIN.

CONCLUSIONS

- The LANDSCAPE and NEST development program represents a broad and flexible clinical development program in patients with MDD and PPD.
- Clinical trials of the LANDSCAPE and NEST programs have consistently reported that patients receiving zuranolone demonstrate significant improvement in depressive symptoms compared with placebo as early as Day 2/3.
- Across 2 of the 3 trials summarized here, patients with MDD or PPD who received a once-daily, 14-day treatment course of zuranolone demonstrated significant improvement in depressive symptoms at Day 15 (primary endpoint of all trials) compared with those who received placebo.
- Across trials and doses to-date, treatment with zuranolone has been generally well-tolerated with a consistent safety and tolerability profile.
- Ongoing LANDSCAPE and NEST studies are investigating zuranolone 50 mg.
- Overall, the data from the completed NEST and LANDSCAPE studies support further development of zuranolone for potential use as a rapidly acting, 2-week treatment for MDD and PPD.

The National Network of Depression Centers (NNDC)
2021 Virtual Conference
September 21st – 22nd, 2021

Zuranolone Clinical Development Program

NEST: ROBIN STUDY; SKYLARK STUDY
LANDSCAPE DEPRESSION STUDIES: MOUNTAIN STUDY; WATERFALL STUDY; SHORELINE STUDY; CORAL STUDY

Initiation Monotherapy or add-on to existing antidepressant therapy

Maintenance Monotherapy or add-on to existing antidepressant therapy

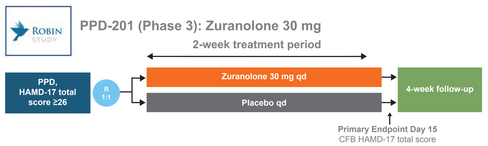
Rapid Response Simultaneous start with antidepressant therapy

	POSTPARTUM DEPRESSION (PPD)		MAJOR DEPRESSIVE DISORDER (MDD)				
STUDY #	**PPD-201**[9] NCT02978326	**PPD-301** NCT04442503	**MDD-201B**[10] NCT03000530	**MDD-301A**[11] NCT03672175	**MDD-301B** NCT04442490	**MDD** NCT03864614	**MDD** NCT04476030
Phase	Phase 3	Phase 3	Phase 2	Phase 3	Phase 3	Phase 3	Phase 3
Design	RCT	RCT	RCT	RCT	RCT	OL	RCT
Population	HAMD-17 ≥26	HAMD-17 ≥26	HAMD-17 ≥22	HAMD-17 ≥22 MADRS ≥32	HAMD-17 ≥24	HAMD MADRS	HAMD
Primary objectives	Efficacy **Zuranolone 30 mg** vs placebo:	Efficacy: **Zuranolone 50 mg** vs placebo	Efficacy **Zuranolone 30 mg** vs placebo:	Efficacy **Zuranolone 30 mg** vs placebo:	Efficacy: **Zuranolone 50 mg** vs placebo	Long-term safety: 1-year follow-up **(Zuranolone 30 mg and 50 mg)***	Efficacy as rapid-response therapy in MDD **Zuranolone 50 mg** + open-label ADT vs placebo + open-label ADT
Primary endpoint	CFB HAMD-17 total score at Day 15	CFB HAMD-17 total score at Day 15	CFB HAMD-17 total score at Day 15	CFB HAMD-17 total score at Day 15	CFB HAMD-17 total score at Day 15	Safety/tolerability at Week 52	CFB HAMD-17 total score at Day 15
Status	Completed	Enrolling	Completed	Completed	Completed	Ongoing	Enrolling

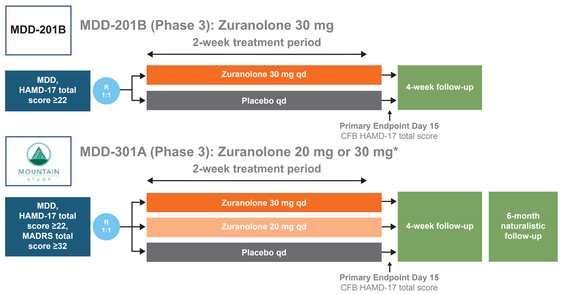
NOTE: The first presentation of the WATERFALL study will be at the 34th European College of Neuropsychopharmacology Congress, October 2-5, 2021.
ADT = antidepressant therapy; CFB = change from baseline; HAMD-17 = 17-item Hamilton Depression Rating Scale; MADRS = Montgomery–Åsberg Depression Rating Scale; MDD = major depressive disorder; OL = open-label; PPD = postpartum depression; RCT = randomized controlled trial; SE = standard error; SOC = standard-of-care.

Study Designs

Completed Nest Program Assessing Safety And Efficacy in Patients With Severe PPD



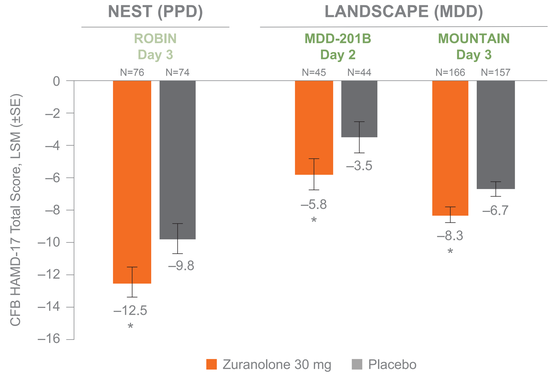
Completed Landscape Programs Assessing Safety and Efficacy in Patients With Moderate to Severe MDD



*NOTE: Data presented here are for the zuranolone 30 mg and placebo arms only.

- Primary Efficacy Endpoint: All studies assessed improvements in depressive symptoms compared with placebo by analyzing the least squares mean (LSM) change from baseline (CFB) in 17-item Hamilton Rating Scale for Depression (HAMD-17) total score at Day 15 after a once-daily, 14-day treatment course of ZRN.
- Day 2 and 3 assessments were secondary endpoints and not adjusted for multiplicity.
- Use of pre-existing antidepressant therapies was permitted provided that patients were on a stable dose prior to and during the study.

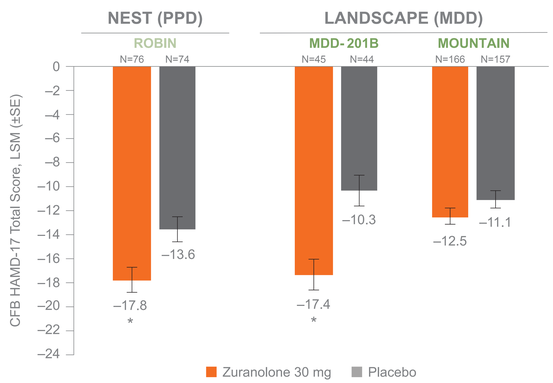
Zuranolone Treatment Led To Rapid (Day 2 or Day 3) and Greater Improvements in Depressive Symptoms Compared With Placebo[9-11]



*p<0.05 vs placebo. p values are nominal and not adjusted for multiplicity.
Note: The clinical trials above differ in sample size, patient population, entry criteria, and study sites, as well as other design elements. No direct comparison can be made across these clinical trials based on the graph above.

- Zuranolone treatment led to rapid improvements in depressive symptoms compared with placebo across clinical trials, with nominally significant improvements observed as early as the first measured time-point (i.e., Day 2 or Day 3).

Zuranolone Treatment Led to Greater Improvements in Depressive Symptoms Compared With Placebo at Day 15 (Primary Endpoints)[9-11]



*p<0.05 vs placebo.
Note: 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.

- At Day 15 (primary endpoint for all trials), significant improvement compared with placebo was observed across 2 of the 3 trials.

Summary of Adverse Events (Incidence of ≥5% in Any Zuranolone Treatment Arm)[9-11]

	PPD		MDD			
	ROBIN		MDD-201B		MOUNTAIN	
Preferred Term, n (%)	**ZRN30 N=78**	**Placebo N=73**	**ZRN30 N=45**	**Placebo N=44**	**ZRN30 N=192**	**Placebo N=190**
Any adverse event	47 (60)	38 (52)	24 (53)	20 (45)	105 (55)	93 (49)
Somnolence	12 (15)	8 (11)	3 (7)	1 (2)	13 (7)	8 (4)
Headache	7 (9)	9 (12)	8 (18)	7 (16)	12 (6)	14 (7)
Dizziness	6 (8)	4 (6)	5 (11)	1 (2)	11 (6)	7 (4)
Upper respiratory tract infection	6 (8)	1 (1)	0	2 (5)	6 (3)	4 (2)
Diarrhea	5 (6)	2 (3)	0	3 (7)	12 (6)	10 (5)
Nausea	3 (4)	6 (8)	5 (11)	1 (2)	7 (4)	9 (5)
Sedation	4 (5)	0	2 (4)	2 (5)	9 (5)	6 (3)

MDD = major depressive disorder; PPD = postpartum depression; ZRN30 = zuranolone 30 mg.

- No adverse events of weight gain, sexual dysfunction, or euphoria were reported in any study; no incidences of loss of consciousness or excessive sedation were observed in any of the trials to date.
- No evidence for increased suicidal ideation or suicidal behavior (measured by the Columbia-Suicide Severity Rating Scale [C-SSRS]) was observed compared with baseline in any study.

References 1. Rush AJ et al. *Am J Psychiatry*. 2006;163(11):1905-17; 2. Romera I et al. *BMC Psychiatry*. 2013;11:13:51; 3. Nock MK et al. *PLoS Med*. 2009;6(8):e1000123; 4. Luscher B et al. *F1000Research*. 2019;8:751; 5. Maguire J. *Front Cell Neurosci*. 2019;13:83; 6. Althaus AL et al. *Neuropharmacology*. 2020; 181:108333; 7. Martinez Botella G et al. *J Med Chem*. 2017;60(18):7810-7819; 8. Hoffmann E et al. *Clin Pharmacokinet*. 2020;59(1):111-120; 9. Deligiannidis KM et al. *JAMA Psychiatry*. 2021 Sep 1;78(9):951-959; 10. Gunduz-Bruce H et al. *N Engl J Med*. 2019;381(10):903-911; 11. Mittal A, et al. Poster presented at the American Academy of Neurology Annual Meeting, Toronto, Canada. April 25-May 1, 2020; 12. Cutler AJ, et al. Poster presented at the American Society of Clinical Psychopharmacology Annual Meeting, Virtual Congress. June 1-4, 2021. Support and Disclosures **AHC** reports grants from Daré Bioscience, Janssen, Praxis Precision Medicines, Relmada Therapeutics, Inc., and Sage Therapeutics, Inc.; consulting fees Fabre-Kramer, Janssen Research & Development, LLC, MindCure, Ovoca Bio plc, Praxis Precision Medicines, PureTech 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, Medifilx LLC, and S1 Biopharma. **AJC** serves as a Consultant to AbbVie, Acadia, AiCure, Alfasigma, Alkermes, Allergan, Cognitive Research, Intra-Cellular Therapies, Janssen, Jazz Pharmaceuticals, Lundbeck, MedAvante-Prophase, Neurocrine, Noven, Otsuka, Sage Therapeutics, Sunovion, Supernus, Takeda, Terran Biosciences, Teva. Dr. Culter serves as Speaker/Promotional Honoraria for AbbVie, Acadia, Alfasigma, Alkermes, Allergan, Intra-Cellular Therapies, Janssen, Lundbeck, Neurocrine, Noven, Otsuka, Sunovion, Supernus, Takeda, Teva. He has received research Grants from Acadia, Alkermes, Allergan, Axsome, Biohaven, Intra-Cellular Therapies, Janssen, Lilly, Lundbeck, Novartis, Otsuka, Sage Therapeutics, Sunovion, Takeda. Dr. Cutler is also an employee and board member for the Neuroscience Education Institute. **KMD** serves as a consultant to Sage Therapeutics, Inc., 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. **RL, CB, AJS, SJK,** and **JD** are employees of Sage Therapeutics, Inc., and hold stock or stock options. ROBIN, MDD-201B, and MOUNTAIN were funded by Sage Therapeutics Inc. WATERFALL was funded by Sage Therapeutics Inc., and Biogen. Medical writing and editorial support were provided by Symbiotix, LLC, and funded by Sage Therapeutics Inc., and Biogen. The authors thank Brian Werneburg for his contributions to these studies.