Relmada Therapeutics Announces Top-line Results from Phase 3 RELIANCE III Trial for REL-1017 as a Monotherapy for the Treatment of Major Depressive Disorder

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RELIANCE I and II Adjunctive MDD Trials Continue to Advance

CORAL GABLES, Fla., Oct. 13, 2022 /PRNewswire/ -- Relmada Therapeutics, Inc. (Nasdaq: RLMD), a late-stage biotechnology company addressing diseases of the central nervous system (CNS), today announced that its RELIANCE III study (REL-1017-303), evaluating REL-1017 in the monotherapy setting for Major Depressive Disorder (MDD), did not achieve its primary endpoint, which was a statistically significant improvement in depression symptoms compared to placebo as measured by the Montgomery-Asberg Depression Rating Scale (MADRS) on Day 28. In the study, the REL-1017 treatment arm showed a

MADRS reduction of 14.8 points at Day 28 versus 13.9 points for the placebo arm, a higher than expected placebo response. Paradoxical results were observed in certain study sites, where placebo dramatically outperformed REL-1017. Relmada is investigating the nature of these results.

REL-1017, which was administered for 28 days to 232 subjects in RELIANCE III, demonstrated very favorable tolerability and safety, confirming the results of Phase 1 and Phase 2 studies (Fava et al, 2022)[1], with no opioid-like effects, no withdrawal effects, and no psychotomimetic effects. There were no adverse events related to QTcF prolongation.

"While these RELIANCE III results are disappointing for patients, the need for new, safe and effective treatments for MDD continues to exist. We look forward to the data from the ongoing RELIANCE I and II trials of REL-1017, a potential new therapy for the adjunctive treatment of MDD." said Maurizio Fava, Psychiatrist-In-Chief, Massachusetts General Hospital and Slater Family Professor of Psychiatry, Harvard Medical School.

To better understand the paradoxical results, a post-hoc, exploratory analysis using the band-pass method (Merlo-Pich et al, 2010[2]) was conducted. The band-pass analysis excludes sites with implausibly high or low placebo responses (defined as a mean decrease from baseline in MADRS10 score greater than 14 and less than 3 points) and showed a meaningful difference between REL-1017 and placebo (>4.9 points on the MADRS, $p<0.05$).

Relmada continues to enroll patients in RELIANCE I and RELIANCE II, two ongoing Phase 3, placebo-controlled, pivotal studies evaluating REL-1017 as a potential adjunctive treatment for MDD. The RELIANCE development program also includes RELIANCE-OLS, a long-term open-label safety study that is enrolling rollover participants from all three pivotal studies, as well as de novo participants.

References

[1]Fava M, Stahl S, Pani L, De Martin S, Pappagallo M, Guidetti C, Alimonti A, Bettini E, Mangano RM, Wessel T, de Somer M, Caron J, Vitolo OV, DiGuglielmo GR, Gilbert A, Mehta H, Kearney M, Mattarei A, Gentilucci M, Folli F, Traversa S, Inturrisi CE, Manfredi PL. REL-1017 (Esmethadone) as Adjunctive Treatment in Patients With Major Depressive Disorder: A Phase 2a Randomized Double-Blind Trial. Am J Psychiatry. 2022 Feb;179(2):122-131. doi: 10.1176/appi.ajp.2021.21020197. Epub 2021 Dec 22. PMID: 34933568.

[2]Merlo-Pich E, Alexander RC, Fava M, Gomeni R. A new population-enrichment strategy to improve efficiency of placebo-controlled clinical trials of antidepressant drugs. Clin Pharmacol Ther. 2010 Nov;88(5):634-42. doi: 10.1038/clpt.2010.159. Epub 2010 Sep 22.

About REL-1017

REL-1017, a new chemical entity (NCE) and novel NMDA receptor (NMDAR) channel blocker that preferentially targets hyperactive channels while maintaining physiological glutamatergic neurotransmission, is currently in late-stage development for the treatment of major depressive disorder (MDD). The ongoing Reliance Clinical Research Program is designed to evaluate the potential for REL-1017 as a rapid-acting, oral, once-daily antidepressant treatment. In a Phase 2 trial, REL-1017 demonstrated rapid, robust, and sustained antidepressant effects with statistically significant improvements compared to placebo. The Phase 2 study also showed a favorable pharmacokinetic, safety, and tolerability profile of REL-1017 consistent with results observed in previously completed Phase 1 studies.

About Relmada Therapeutics, Inc.

Relmada Therapeutics is a late-stage biotechnology company addressing diseases of the central nervous system (CNS), with focus on major depressive disorder (MDD). Relmada's experienced and dedicated team is committed to making a difference in the lives of patients and their families. Relmada's lead program, REL-1017, is a new chemical entity (NCE) and novel NMDA receptor (NMDAR) channel blocker that preferentially targets hyperactive channels while maintaining physiological

glutamatergic neurotransmission. REL-1017 has entered late-stage development as an adjunctive treatment for MDD in adults. In addition, Relmada is advancing a clinical-stage program in neurodegenerative diseases based on psilocybin and select derivative molecules. Learn more at www.relmada.com.

Forward-Looking Statements

The Private Securities Litigation Reform Act of 1995 provides a safe harbor for forward-looking statements made by us or on our behalf. This press release contains statements which constitute "forward-looking statements" within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. Any statement that is not historical in nature is a forward-looking statement and may be identified by the use of words and phrases such as "expects," "anticipates," "believes," "will," "will likely result," "will continue," "plans to," "potential," "promising," and similar expressions. These statements are based on management's current expectations and beliefs and are subject to a number of risks, uncertainties and assumptions that could cause actual results to differ materially from those described in the forward-looking statements, including potential failure of RELIANCE trial results to demonstrate clinically significant evidence of efficacy and/or safety, failure of top-line results to accurately reflect the complete results of the trial, failure to obtain regulatory approval of REL-1017 for the treatment of major depressive disorder, and the other risk factors described under the heading "Risk Factors" set forth in the Company's reports filed with the SEC from time to time. No forward-looking statement can be guaranteed, and actual results may differ materially from those projected. Relmada undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events, or otherwise. Readers are cautioned that it is not possible to predict or identify all the risks, uncertainties and other factors that may affect future results and that the risks described herein should not be a complete list.

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