December 7, 2022

Relmada Therapeutics Announces Top-line Results from Phase 3 RELIANCE I Trial for REL-1017 as an Adjunctive Treatment for Major Depressive Disorder

Company to Host Conference Call Today, December 7, 2022, at 5:00 PM ET

CORAL GABLES, Fla., Dec. 7, 2022 /PRNewswire/ -- Relmada Therapeutics, Inc. (Nasdaq: RLMD), a late-stage biotechnology company addressing diseases of the central nervous system (CNS), today announced results of the RELIANCE I study (REL-1017-301), evaluating REL-1017 as an adjunctive treatment for Major Depressive Disorder (MDD). The same factors that negatively affected the previously announced results from the RELIANCE III study, a limited number of high enrolling sites with unplausible placebo response, also affected RELIANCE I and the study 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. RELIANCE I evaluated the use of REL-1017 in addition to a standard antidepressant for patients who had inadequate response to at least one and up to three standard antidepressant therapies.

In the study, the REL-1017 treatment arm (n= 113) showed a MADRS reduction of 15.1 points at Day 28 versus 12.9 points for the placebo arm (n=114), which is a clinically meaningful difference of 2.2 points on the MADRS, as well as a statistically significant difference in the response rate, with a response rate of 27.2% on placebo vs 39.8% in the REL1017 arm ($p<0.05$).

As was observed in the monotherapy study RELIANCE III (Study 303), implausible results were again observed in two of the same high enrolling RELIANCE I (Study 301) study centers, where placebo dramatically outperformed REL-1017. While the patient population in RELIANCE I was different than RELIANCE III in that subjects enrolled should already have been diagnosed with depression and did not respond adequately to at least one, and up to three courses of antidepressant therapy, a limited number of the same high enrolling centers had implausible rapid and sustained placebo response rates that outperformed REL1017.

In a post-hoc analysis of RELIANCE 1 (301 Study) that excluded the same two high enrolling centers that showed implausible placebo response in both REL-1017 studies, the REL-1017

treatment arm (n=97) showed a MADRS reduction of 16.7 points at Day 28 versus 12.6 points for the placebo arm (n=88), a 4.1 point difference, with a $p<0.02$.

A second post-hoc confirmatory analysis, using the well-established band-pass method (Merlo-Pich et al, 2010[1]), that excludes patients from those centers with implausible responses in the placebo arm (centers with a placebo response less than 3% from baseline and more than 33% from baseline) showed a robust difference between REL-1017 and placebo.

REL-1017, as it did in RELIANCE III, demonstrated very favorable tolerability and safety in RELIANCE I, again confirming the results of Phase 1 and Phase 2 studies (Fava et al, 2022[2]), with no opioid-like effects, no withdrawal effects, and no psychotomimetic effects.

Relmada continues to enroll patients in RELIANCE II, the second ongoing Phase 3, two-arm, placebo-controlled, pivotal study evaluating REL-1017 as a potential adjunctive treatment for MDD. Based on the results of RELIANCE I and RELIANCE III, Relmada is applying several protocol and operational changes to RELIANCE II and making certain improvements to how the trial is being conducted. The RELIANCE development program also includes RELIANCE-OLS, a long-term open-label safety study that is evaluating rollover participants from all three pivotal studies, as well as de novo participants.

Conference Call and Webcast Information

Relmada will host a conference call and webcast presentation today, December 7, 2022, at 5:00 PM Eastern Time to discuss the study results, which can be accessed with the information below:

Wednesday, December 7, 2022, at 5:00 PM ET

Domestic: 1-877-407-0792
International: 1-201-689-8263
Conference ID: 13734757
Webcast: https://viavid.webcasts.com/starthere.jsp?ei=1586761&tp_key=6ce3a6bfd7

The subsequent archived recording will be available on the Investors section of the Relmada website at www.relmada.com.

References

[1]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.

[2]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.

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 is in 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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