February 23, 2022

Relmada Therapeutics Announces Top-Line Results of Study Evaluating REL-1017 vs Ketamine for Abuse Potential

- All doses of REL-1017, including the maximum tolerated dose, demonstrated a statistically significant difference in abuse potential vs. ketamine (p-values <0.05)

- All doses of REL-1017, including the maximum tolerated dose, were statistically equivalent to placebo (p-values <0.05)

- Company to host conference call at 8:30 AM Eastern Time today, February 23, 2022

CORAL GABLES, Fla., Feb. 23, 2022 /PRNewswire/ -- Relmada Therapeutics, Inc. (NASDAQ: RLMD), a late-stage biotechnology company addressing diseases of the central nervous system (CNS), today announced top-line results of the human abuse potential (HAP) study with REL-1017, a novel NMDA receptor (NMDAR) channel blocker and the company's lead candidate in Phase 3 development for the treatment major depressive disorder (MDD).

Top-line results showed that all three doses of REL-1017 (25 mg, 75 mg, and 150 mg, the therapeutic, supratherapeutic and maximum tolerated doses, respectively) tested in recreational drug users, demonstrated a substantial (30+ points) and statistically significant difference vs. the active control drug, intravenous ketamine 0.5 mg/kg over 40 minutes, and were statistically equivalent to placebo. The study's primary endpoint was a measure of "likability" with the subjects rating the maximum effect (or Emax) for Drug Liking "at this moment", using a 1-100 bipolar rating scale (known as a visual analog scale or VAS), with 100 as the highest likability, 50 as neutral (placebo-like), and 0 the highest dislike. Consistent results are seen for the secondary endpoints. Results of the primary endpoint are summarized in the table below.

	Placebo	REL-1017 25 mg	REL-1017 75 mg	REL-1017 150 mg	Ketamine 0.5 mg/kg
Mean Emax for Drug Liking	50.9	51.4	54.9	59.2	90.0
P-value for REL-1017 Difference vs ketamine 0.5 mg/Kg over 40 minutes	<0.05	<0.05	<0.05	<0.05	-

P-value for REL-1017 Difference vs. placebo	-	<0.05	<0.05	<0.05	<0.05

"These results demonstrate that REL-1017 strongly differentiates from ketamine and is comparable to placebo for the maximum effect for Drug Liking 'at this moment," said Sergio Traversa, CEO of Relmada Therapeutics. "Importantly, these data are consistent with previously generated results of the REL-1017 vs. oxycodone HAP study, which showed no meaningful abuse potential on the opioid domain. With the ketamine comparative study, we completed the extensive abuse potential testing program in line with the FDA 2017 published guidance. These collective results confirm the previously published data and the DEA statement that esmethadone does not have meaningful abuse potential.

Paolo Manfredi, M.D., Chief Scientific Officer of Relmada said, "We are very satisfied with the results of our second confirmatory HAP study, designed following FDA guidance, as part of the planned New Drug Application for REL-1017 for the treatment of MDD. These data are consistent with our prior oxycodone HAP study and confirm the large body of literature indicating the lack of meaningful abuse potential of REL-1017. There is a significant need for new treatment options for patients suffering from depression, and we continue to believe that REL-1017 has the potential to be a very safe, well tolerated and effective rapid acting antidepressant."

Jack Henningfield, Ph.D., Vice President, Research, Health Policy, and Abuse Liability at Pinney Associates and former Chief of the Clinical Pharmacology Research Branch and the Abuse Potential and Biology of Dependence Assessment Section of the National Institute on Drug Abuse (NIDA), added, "These data show no evidence of meaningful abuse potential of REL-1017 compared to ketamine, including at the maximum tolerated dose with a likability profile comparable to placebo. These ketamine data and the previously released oxycodone data are consistent with HAP study results of other approved products that are unscheduled or in Schedule V."

Conference Call and Webcast Information

Relmada will host a conference call and webcast presentation today, February 23, 2022, at 8:30 AM Eastern Time to discuss the study results, which can be accessed with the information below:

Wednesday, February 23 at 8:30 AM ET

Domestic: 1-866-409-1555
International: 1-313-209-4906
Conference ID: 1751730
Webcast: https://viavid.webcasts.com/starthere.jsp?ei=1532206&tp_key=c85c506a7e

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

Background

REL-1017 (which is also known as esmethadone, dextromethadone, or d-methadone), is the opioid-inactive, dextro- or right-side isomer of racemic methadone. Prior preclinical and clinical findings have indicated that the dextro-isomer, REL-1017, lacks the addiction liability

and respiratory depressant effects of its parent molecule. In contrast, levomethadone, the left-side isomer, is an opioid agonist and is entirely responsible for the analgesic activity of the parent molecule.[1]

HAP studies are conducted to evaluate the likelihood that a medicine affecting the central nervous system may be abused by patients or the general public. The study comparing REL-1017 to ketamine is the second of two clinical trials to assess abuse potential per FDA guidance as part of the planned REL-1017 NDA for the treatment of MDD.

The scheduling of a drug depends on the analysis of several parameters (receptor studies, animal studies, human studies, history of abuse). These parameters are generally referred to as the "eight factor analysis". All tested parameters suggest a lack of any meaningful abuse potential for REL-1017 and are fully aligned with the 2019 DEA statement on methadone.[1]

About The Human Abuse Potential Study for REL-1017 vs. Ketamine

The study was a single-dose, Phase 1, randomized, double-blind, double-dummy, active- and placebo-controlled, six-way crossover study to assess the abuse potential of REL-1017 relative to ketamine and placebo in healthy experienced recreational drug users. Ketamine, the active control, was administered intravenously at the dose of 0.5 mg/kg, a standard dose in HAP studies. A total of 51 subjects were enrolled and fulfilled criteria for the predefined statistical analysis.

Once available, the full data set and detailed results will be submitted to the FDA and for presentation at future scientific conferences and publication in peer-reviewed journals.

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 MDD in adjunctive and monotherapy Phase 3 studies. The ongoing RELIANCE Phase 3 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 in tested measures of depression. The Phase 2 study also showed a favorable safety, tolerability, and pharmacokinetics profile of REL-1017, consistent with 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 a 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 and monotherapy 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, including but not limited to statements regarding the effectiveness of REL-1017, or its potential approval by the FDA, for treatment of MDD or any other indication, or of the safety, tolerability, effectiveness or potential for approval of psilocybin or derivative molecules for any indication. Any statement that is not historical in nature is a forward-looking statement. These may, but will not always, 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 the 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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1. DEA: Diversion Control Division. December 2019. Accessed May 2020. https://www.deadiversion.usdoj.gov/drug_chem_info/methadone/methadone.pdf

View original content to download multimedia:https://www.prnewswire.com/news-releases/relmada-therapeutics-announces-top-line-results-of-study-evaluating-rel-1017-vs-ketamine-for-abuse-potential-301488462.html

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