UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT

Pursuant to Section 13 or 15(d) of the
Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): **December 7, 2021**

RELMADA THERAPEUTICS, INC.
(Exact name of registrant as specified in its charter)

Nevada	**001-39082**	**45-5401931**
(State or other jurisdiction of incorporation)	(Commission File Number)	(IRS Employer Identification No.)

2222 Ponce de Leon Blvd., Floor 3 Coral Gables, FL	**33134**
(Address of principal executive offices)	(Zip Code)

Registrant's telephone number, including area code **(786) 629-1376**

N/A
(Former name or former address, if changed since last report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (see General Instruction A.2. below):

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	**Trading Symbol**	**Name of exchange on which registered**
Common stock, $0.001 par value per share	**RLMD**	**The NASDAQ Stock Market LLC**

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 8.01 Other Events.

On December 7, 2021, Relmada Therapeutics, Inc. (the "Company") made a poster presentation at the American College of Neuropsychopharmacology (ACNP) 60th annual meeting regarding results of the Company's Human Abuse Potential (HAP) study of REL-1017 (esmethadone).

A copy of the poster presentation is filed herewith as Exhibit 99.1 and is incorporated herein by reference.

Item 9.01. Financial Statements and Exhibits.

(d) Exhibits

Exhibit No.	**Description**
99.1	Relmada Therapeutics, Inc. Poster Presentation
104	Cover Page Interactive Data File (formatted as Inline XBRL)

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Dated: December 7, 2021

RELMADA THERAPEUTICS, INC.

By: */s/ Sergio Traversa*
Name: Sergio Traversa
Title: Chief Executive Officer

No Meaningful Opioid Abuse Liability of REL-1017 (esmethadone; d-methadone), a Rapid-Acting Antidepressant in Clinical Development: A Human Abuse Potential Study

Jack Henningfield[1]; Glen Aqaloff[2]; Charles Gorodetzky[1,3]; Marco Pappagallo[3,4]; Megan Shram[5]; Sara De Martin[5]; Reginald Fant[5]; Frank Vocci[1,6]; Frank Sapienza[1,6]; Thomas Kosten[1,6]; Jeff Huston[7]; August Buchhalter[7]; Judy Ashworth[7]; Ryan Lanier[7]; Franco Folli[8]; Sergio Traversa[9]; Charles E Inturrisi[9]; Paolo L. Manfredi[9]

1 Pinney Associates, Bethesda, MD, USA; 2 Ohio Clinical Trials, Columbus, OH, USA; 3 Relmada Therapeutics, Inc, Coral Gables, FL, USA; 4 Consultant in Pharmacokinetic Medicine; 5 Department of Anesthesiology, Albert Einstein College of Medicine, Bronx, NY, USA; 6 Alkahest Research Partners, Toronto, ON, Canada; 7 Department of Pharmaceutical and Pharmacological Sciences, University of Padova, Padova, Italy; 8 Florida Research Institute, Baltimore, MD; 9 The Drug and Chemical Advisory Group LLC, Fairfax, VA, USA; 10 Baylor College of Medicine, MD Anderson Cancer Center, U of Houston, Michael E DeBakey VA Medical Center, Houston, TX, USA; 11 University of Milano School of Medicine, Milan, Italy

INTRODUCTION

- REL-1017 (esmethadone; d-methadone) is a safe and well tolerated[1] novel uncompetitive NMDAR channel blocker with a preference for pathologically hyperactive GluN1-GluN2D NMDAR channels[2].
- REL-1017 has twenty-fold lower affinity at the mu-opioid receptor than levo-methadone [3] and lacks clinically meaningful opioid agonist actions[4-7].
- REL-1017 retains potential neuroplasticity and therapeutic effects without dissociative effects[1,4,8,9] and does not cause potentially neurotoxic Olney's brain lesions[4], unlike higher potency NMDAR blockers.
- REL-1017 is currently in Phase 3 clinical trials for the treatment of Major Depressive Disorder (MDD)[10].
- Preclinical data performed with well-established experimental models, indicated that REL-1017 did not show any appreciable evidence of abuse potential[11,12].
- Due to its close chemical similarity to the opioid-active isomer, l-methadone, we further evaluated REL-1017 with a human abuse potential (HAP) study.

OBJECTIVES

We aimed to assess the human abuse potential (HAP) of REL-1017 in a single-dose, randomized, double-blind, double-dummy, active- and placebo-controlled, 5-way crossover study in experienced recreational drug users.

METHODS

Study Design:

- Single-dose, randomized, double-blind, double-dummy, active- and placebo-controlled, 5-way crossover HAP study of REL-1017 in experienced recreational drug users.

Each subject received the following oral treatments with >=11 days of washout between treatments: REL-1017 25 mg (therapeutic daily dose), REL-1017 75 mg (loading dose), REL-1017 150 mg (6x the therapeutic daily dose and the maximum tolerated dose), Oxycodone 40 mg (standard active control), and placebo.

Endpoint Measurements:

- The primary endpoint of the study was the maximum effect (E_{max}) for Drug Liking ("at this moment"), assessed with a bipolar (0 to 49 = dislike; 50 = neutral; 51-100 = like) visual analog scale (VAS).
- Key secondary endpoints were "Overall Drug Liking" and for "Take Drug Again", assessed with a bipolar (0 to 49 = dislike; 50 = neutral; 51-100 = like) VAS.

Data Analysis:

Data for the primary endpoint were analyzed using a one-sided paired Student's t-test (if data were not skewed) or Sign Test (if data were skewed). For primary endpoint analysis (Table 2), comparisons were made (at α=0.05):

- between Oxycodone 40 mg and placebo (null hypothesis that the difference between Oxycodone 40 mg and placebo was ≤ 15 points);
- between Oxycodone 40 mg and each dose of REL-1017 (null hypothesis that the difference between Oxycodone 40 mg and REL-1017 was ≤ 0 points), and
- between each dose of REL-1017 and placebo (null hypothesis that the difference between REL-1017 and placebo was ≥ 15 points).

The methods and hypotheses for the secondary endpoints were similar to that of the primary endpoint, except margins of 0 were used for all test hypotheses and for the third hypothesis (comparison between REL-1017 and placebo), a two-sided hypothesis with α=0.1 was utilized (null hypothesis that the difference between REL-1017 and placebo equals 0).

Statistical analyses were performed on "modified completers", defined as subjects completing all 5 treatments, and excluding subjects with similar Drug Liking E_{max} scores (<5 points difference) across all study treatments or subjects with an E_{max} for placebo >60 and ≤5 difference between E_{max} for Oxycodone 40 mg and placebo.

No Meaningful Opioid Abuse Liability of REL-1017 (esmethadone; d-methadone)

RESULTS

Table 1.
Baseline demographic characteristics (Modified completers, N=44)

Demographics		Overall (N=44) N (%)
Age, mean ± (SD), years		36.6 (9.2)
Gender		
	Male	36 (81.8%)
	Female	8 (18.2%)
Race		
	Black / African American	25 (56.8%)
	White	19 (43.2%)
Ethnicity		
	Hispanic or Latino	5 (11.4%)
	Not Hispanic or Latino	39 (88.6%)

Table 2.
Drug Liking (E_{max}) "at this moment" bipolar Visual Analog Scale (VAS): Primary endpoint

Drug Liking (E_{max}) "at this moment" (VAS)**	Placebo N=44	REL-1017 25 mg N=44	REL-1017 75 mg N=44	REL-1017 150 mg N=44	Oxycodone 40 mg N=44
Mean (SD)	51.7 (4.3)	53 (8.7)	58.2 (15.0)	64.9 (16.7)	85 (15.4)
Median	50	50	50	58	89
Treatment vs Oxycodone 40mg, P-value	<0.001	<0.001	<0.001	<0.001	--
REL-1017 vs Placebo, P-value ‡	--	<0.001	<0.001	0.082	--

** The primary endpoint of the study was the maximum effect (E_{max}) for Drug Liking ("at this moment"), assessed with a bipolar (0 to 49 = dislike; 50 = neutral; 51-100 = like) visual analog scale (VAS).

‡ Interpretation of P-value: P-value ≥0.05 suggests that REL-1017 has similar abuse potential to placebo (i.e., within 5 points).

- The E_{max} for Oxycodone 40 mg was significantly greater than placebo, confirming study validity.
- The E_{max} for Oxycodone 40 mg was greater than all 3 doses of REL-1017 (p<0.001).
- Comparison of REL-1017 to placebo, using the FDA suggested equivalence analysis, indicated similarity to placebo at P<0.001 for REL-1017 25 mg and REL-1017 75 mg. REL-1017 150 mg showed P=0.082 for similarity to placebo.

Table 3.
Overall Drug Liking bipolar Visual Analog Scale (VAS): Key secondary endpoint

Overall Drug Liking VAS	Placebo N=44	REL-1017 25 mg N=44	REL-1017 75 mg N=44	REL-1017 150 mg N=44	Oxycodone 40 mg N=44
Mean (SD)	51.3 (10.9)	51.9 (7.0)	58.5 (19.5)	61.5 (18.8)	75.1 (23.1)
Median	50.0	50.0	50.0	50.5	73.5
Treatment vs Oxycodone 40mg, P-value	<0.001	<0.001	<0.001	<0.002	--
REL-1017 vs Placebo, P-value	--	0.793	>0.999	0.029	--

Table 4.
Take Drug Again bipolar Visual Analog Scale (VAS): Key secondary endpoint

Take Drug Again VAS	Placebo N=44	REL-1017 25 mg N=44	REL-1017 75 mg N=44	REL-1017 150 mg N=44	Oxycodone 40 mg N=44
Mean (SD)	49.7 (15.7)	51.1 (16.3)	57.7 (23.8)	61.3 (25.4)	77.1 (25.9)
Median	50.0	50.0	50.0	50.0	86.0
Treatment vs Oxycodone 40mg, P-value	<0.001	<0.001	<0.001	0.002	--
REL-1017 vs Placebo, P-value	--	0.664	0.230	0.006	--

- Statistically significant differences between all tested doses of REL-1017 and Oxycodone were seen for the two key secondary endpoints (see Tables 3 and 4).
- Comparison of REL-1017 to placebo showed that REL-1017 25 mg and REL-1017 75 mg were not significantly different from placebo (P-values >0.10) and REL-1017 150 mg was significantly different from placebo (P-values <0.10) for "Overall Drug Liking" and "Take Drug Again".

CONCLUSIONS

- In this study, all REL-1017 tested doses exhibited at least a 20-point difference in mean and median Drug Liking E_{max} compared to Oxycodone (p<0.001) among recreational drug users.
- The similarity of REL-1017 25 mg and REL-1017 75 mg in Drug Liking E_{max} ("at this moment") compared to placebo was significant (P <0.001).
- Comparable results of REL-1017 vs Oxycodone and REL-1017 vs Placebo were observed for the two key secondary endpoints ("Overall Drug Liking" and "Take Drug Again").
- Low-level liking, commonly seen in HAP studies at high doses of the test substance, is consistent with unscheduled substances and with controlled substances in U.S. DEA Schedule V or IV[13].
- This study showed no meaningful opioid abuse potential for REL-1017. This HAP study design is considered the most predictive for determining opioid abuse potential.

REFERENCES

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DISCLOSURES

This research was sponsored by Relmada Therapeutics. Drs. Aqaloff and Huston are employees at Ohio Clinical Trials. Drs. Henningfield, Gorodetzky, Shram, Buchhalter, Ashworth, Lanier, Vocci, Sapienza, Kosten, Folli, Pappagallo, Inturrisi, and Manfredi are paid consultants for Relmada Therapeutics. Dr. Traversa is a current employee of Relmada Therapeutics. Dr. De Martin is employed or has received fees from companies or Universities that have received payments or grants from Relmada. Drs. Inturrisi and Manfredi are inventors on esmethadone patents and other patents and patent applications. "We are grateful for the contributions of Dr. Reginald ("Reggie") Fant. We were deeply saddened by his unexpected death in September 2020.

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American College of Neuropsychopharmacology (ACNP)
60th Annual Meeting, December 5-8, 2021