No meaningful abuse potential in recreational opioid users of REL-1017 (esmethadone hydrochloride), a new NMDAR antagonist and potential rapid-acting antidepressant

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INTRODUCTION

- REL-1017 (esmethadone hydrochloride) 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 does not cause dissociative effects[1,4,5,6,7,8] and does not cause potentially neurotoxic Olney's brain lesions[9], unlike higher potency NMDAR blockers
- REL-1017 showed rapid, robust and sustained antidepressant effects as adjunctive treatment in patients with MDD[8]
- REL-1017 is currently in Phase 3 clinical trials for the treatment of Major Depressive Disorder (MDD)[10]
- Preclinical experimental models indicate that REL-1017 does not have abuse potential[11,12,13]
- Due to its close chemical similarity to the opioid-active isomer, l-methadone, we further evaluated REL-1017 in a human abuse potential (HAP) study in experienced recreational opioid users

OBJECTIVE

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 opioid 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 opioid 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 (3X the therapeutic and 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 "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 ≥ 11 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.
Statistical analyses were performed on the "Completer Population", defined as subjects completing all 5 treatments.

RESULTS

Table 1. Baseline demographic characteristics, Completer Population N=47

Demographics		Overall (N=47) N (%)
Age, mean ± (SD), years		36.3 (9.13)
Gender		
	Male	37 (78.7.%)
	Female	10 (21.3%)
Race		
	Black / African American	27 (57.4%)
	White	20 (42.6%)
Ethnicity		
	Hispanic or Latino	5 (10.6%)
	Not Hispanic or Latino	42 (89.4%)

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=47	REL-1017 25 mg N=47	REL-1017 75 mg N=47	REL-1017 150 mg N=47	Oxycodone 40 mg N=47
Mean (SD)	52.7 (6.5)	54.2 (10.3)	58.7 (15.0)	64.9 (16.6)	83.2 (16.6)
Median	50	50	50	58	85
oxycodone 40 mg vs REL-1017 (difference), p-value	<0.001	<0.001	<0.001	<0.001	--
REL-1017 vs Placebo (equivalence), p-value#	--	<0.001	<0.001	0.036	--

++ 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-values ≤0.05 indicate that REL-1017 is statistically equivalent to placebo (i.e., within 11 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<0.05 at all tested doses.

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

Overall Drug Liking VAS	Placebo N=47	REL-1017 25 mg N=47	REL-1017 75 mg N=47	REL-1017 150 mg N=47	Oxycodone 40 mg N=47
Mean (SD)	52.6 (12.5)	53.1 (9.2)	58.1 (19.3)	61.4 (18.7)	73.9 (24)
Median	50.0	50.0	50.0	51	73
oxycodone 40 mg vs REL-1017 (difference), p-value	<0.001	<0.001	<0.001	0.004	--

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

Take Drug Again VAS	Placebo N=47	REL-1017 25 mg N=47	REL-1017 75 mg N=47	REL-1017 150 mg N=47	Oxycodone 40 mg N=47
Mean (SD)	51.1 (16.7)	52.6(17.3)	57.8 (24.3)	61.2 (22.9)	76.1 (27)
Median	50.0	50.0	50.0	50.0	83.0
oxycodone 40 mg vs REL-1017 (difference), p-value	<0.001	<0.001	<0.001	0.002	--

- 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).

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 (primary endpoint).**
- **All REL-1017 were statistically equivalent to placebo for Drug Liking E_{max} ("at this moment") (p<0.05).**
- **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").**
- **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

1. Bernstein, G., et al. (2019). J Clin Psychopharmacol 39(3): 226-237.
2. Bettini, E., et al., (2021) Biological Psychiatry, 89(9), S198-S199.
3. Codd, E. E., et al. (1995). J Pharmacol Exp Ther 274(3): 1263-1270.
4. Lemberg, K. et al (2006). Anesth Analg. 102(6):1768-74.
5. Isbell H, Eisenman AJ (1948). J Pharmacol Exp Ther 93(3):305–1.
6. Drug Enforcement Administration. Diversion Control Division. December 2019.
7. Fraser & Isbell (1962). Bulletin on Narcotics, 14: 25-35.
8. Fava, M., et al. (2022). American Journal of Psychiatry 179(2):122-131.
9. Pappagallo, M. et al (2021) The FASEB Journal, 35
10. ClinicalTrials.gov Identifier: NCT04855747; NCT04688164
11. Henningfield, J., et al. (2021) Poster Presented at NEI 2021
12. Henningfield J., et al. (2021) Poster Presented at CPDD 2021
13. Gauvin, D., et al. (2021) Poster Presented at CPDD 2021

DISCLOSURES

Inturrisi, Manfredi and Pappagallo contributed equally. This research was sponsored by Relmada Therapeutics. Drs. Apseloff 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.
Previously reported results for this study analyzed the Modified Completer Population (44 subjects) instead of the Completer Population (47 patients).

Relmada THERAPEUTICS

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