REL-1017 (esmethadone hydrochloride), a potential rapid-acting antidepressant has no meaningful opioid abuse potential in non-clinical and clinical abuse potential studies

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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]
- Non-clinical experimental models indicate that REL-1017 did not show evidence of abuse potential[11,12,13]
- Due to its close chemical similarity to the opioid-active isomer, l-methadone, we further evaluated REL-1017 in non-clinical (rat) and human abuse potential (HAP) studies
- This HAP study design is considered the most predictive for determining opioid abuse potential[14]

OBJECTIVE

We aimed to assess abuse potential of REL-1017 in both non-clinical (rat) and human abuse potential (HAP) studies. To this end, we performed experiments in rat models to test drug abuse potential and withdrawal signs. We also tested the abuse potential of REL-1017 in experienced recreational substance users.

METHODS

Non-clinical self-administration study design: Intravenous self-administration of saline, vehicle, oxycodone, or increasing doses of REL-1017: 0.032, 0.056, 0.1 and 0.18 mg/kg/inj (6 rats/group).

Non-clinical withdrawal study design: 9-day drug withdrawal assessment after 30 consecutive days administration by oral gavage of: saline, REL-1017 (62.5 or 100 mg/kg), ketamine (200 mg/kg) or morphine (300 mg/kg). N =16 rats/group.

HAP study design: Single-dose, randomized, double-blind, double-dummy, active- and placebo-controlled, 5-way crossover 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 (daily therapeutic dose), REL-1017 75 mg (3X the therapeutic dose and the loading dose), REL-1017 150 mg (6x the daily therapeutic 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 E_{max} for "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.

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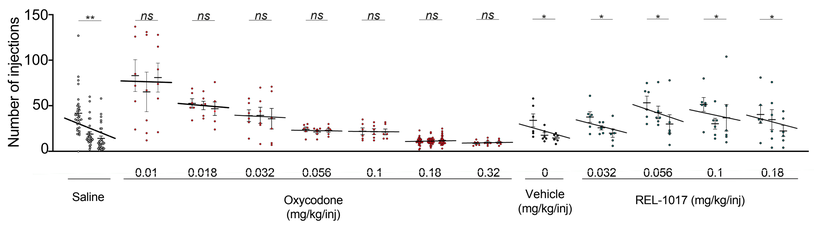
NON-CLINICAL ABUSE POTENTIAL RESULTS

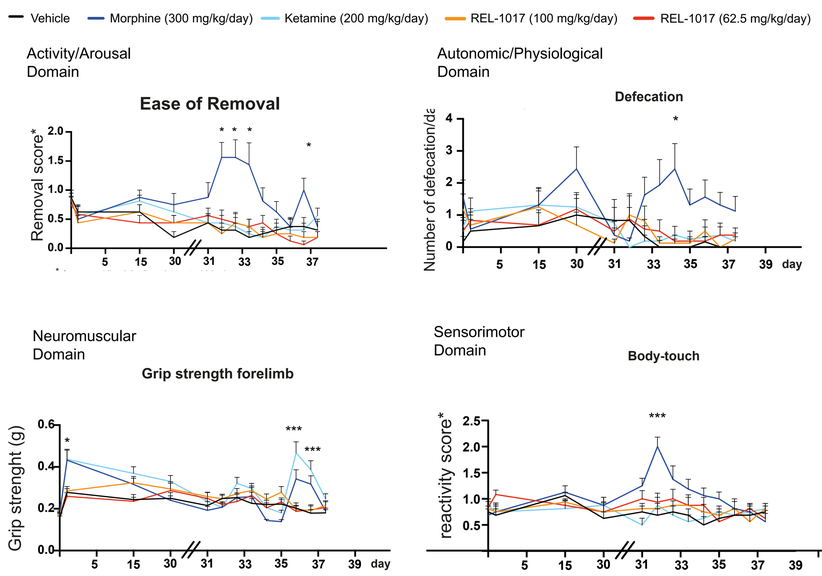
Figure 1. Self-administration study (to test reinforcing effects in rats)



In animals with stable self-administration of oxycodone for the previous 3 days, test sessions were instituted where oxycodone was substituted with: saline; oxycodone (0.01; 0.018; 0.032; 0.056; 0.1; 0.18; 0.32 mg/kg/injection); vehicle; or REL-1017 (0.032; 0.056; 0.1 and 0.18 mg/kg/injection). All rats in the oxycodone tested groups maintained self-administration over the 3-day test period (p=ns between injections at day 1 and 3 for each dose level).

As expected for non-reinforcing stimuli in this assay, saline, vehicle, and all REL-1017 doses showed a typical "extinction burst" pattern of responding, characterized by an initial rapid increase of lever-pressing on the first day followed by a downward staircase pattern of responses on the second and third day (*=p<0.05, **=p<0.01 between injections at day 1 and 3 for all dosing groups, including the vehicle group; n=6 for each group). REL-1017 at all tested doses showed a pattern comparable to vehicle.

Figure 2. Withdrawal study (to test withdrawal signs in rats)



Upon abrupt discontinuation following 30-days of 300 mg/kg/day of morphine, rats exhibited a constellation of changes characteristic of the classic opioid withdrawal-syndrome. As expected, the withdrawal syndrome engendered by morphine spans across multiple domains. Upon abrupt discontinuation following 30-days of 200 mg/kg/day ketamine, rats exhibited a cluster of behavioural changes, as expected for this drug. The testing batteries employed in this study were adequate to identify opiate-type and PCP-type physical dependence and withdrawal. Upon abrupt discontinuation following 30-days of 62.5 and 100 mg/kg/day REL-1017, REL-1017 treated rats did not show neither morphine-type nor ketamine-type discontinuation syndromes.

CLINICAL ABUSE POTENTIAL RESULTS

Table 1. Baseline demographic characteristics in completer population

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%)
Opioid use history*		
	# of times used in lifetime, mean ± (SD)	156.9 (430.86)
	# of times used in the past 12 weeks, mean ± (SD)	7.8 (9.51)

*The statistics for the history of recreational opioid use are based on the safety population (n=50)

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). All REL-1017 tested doses exhibited at least a 19-point median intra-participant difference in Drug Liking E_{max} (primary endpoint) compared to oxycodone.
- 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

- **The non-clinical studies in rats showed that REL-1017 was non-reinforcing and did not demonstrate neither morphine-type nor ketamine-type discontinuation syndrome.**
- **In this HAP study among recreational opioid users, REL-1017 25 mg (daily therapeutic dose), REL-1017 75 mg (3X the therapeutic dose), REL-1017 150 mg (6x the daily therapeutic dose and the maximum tolerated dose) were statistically significantly different from oxycodone 40mg in Drug Liking E_{max} (primary endpoint) (p<0.001) in the completer population.**
- **All REL-1017 doses were statistically equivalent to placebo for the primary endpoint (p<0.05) in the completer population.**
- **Consistent results were observed for the two key secondary endpoints ("Overall Drug Liking" and "Take Drug Again") and for all other secondary endpoints.**
- **These non-clinical (rat) and HAP (human) data indicate that REL-1017 has no meaningful abuse potential, in alignment with a recent DEA statement: "The d-isomer lacks significant respiratory depressant action and addiction liability..."** [15]

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. Dr. Francesco Bifari has no conflict of interest. Drs. Inturrisi and Manfredi are inventors on esmethadone patents and other patents and patent applications. Previously reported results for the HAP study analyzed the Modified Completer Population (44 subjects) instead of the Completer Population (47 patients).

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Henningfield and Shram contributed equally to this research