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

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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 [1,4,5,6,7,8] and does not cause potentially neurotoxic Olney's brain lesions [9], 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 [11,12,13].
- 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 ≥ 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 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.

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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 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<0.001 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)	51.8 (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 (23.4)	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	0.004	--

- 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 [14].
- 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.

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DISCLOSURES

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