No meaningful abuse potential in recreational ketamine 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 mechanism of action as a novel uncompetitive NMDAR channel blocker, we further evaluated REL-1017 in a human abuse potential (HAP) study in experienced recreational ketamine users. This HAP study design is considered the most predictive for determining abuse potential[14]

OBJECTIVE

We aimed to assess the human abuse potential (HAP) of REL-1017 in a single-dose, randomized, double-blind, triple-dummy, active- and placebo-controlled, 6-way crossover study in experienced recreational ketamine users. The dextromethorphan arm was included as an exploratory endpoint.

METHODS

Study Design:

- Single-dose, randomized, double-blind, triple-dummy, active- and placebo-controlled, 6-way crossover HAP study of REL-1017 in experienced recreational ketamine users.
- Each subject received the following oral treatments with >=11 days of washout between treatments: REL-1017 25 mg po (therapeutic daily dose), REL-1017 75 mg po (3X therapeutic and loading dose), REL-1017 150 mg po (6x therapeutic daily dose and the maximum tolerated dose), dextromethorphan 300 mg po, ketamine 0.5 mg/ kg IV administered for 40 minutes (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 IV ketamine .5 mg/kg and placebo (null hypothesis that the difference between ketamine and placebo was ≤ 15 points)
- Between IV ketamine .5 mg/kg and each dose of REL-1017 (null hypothesis that the difference between ketamine and REL-1017 was ≤ 0 points)
- 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 6 treatments.

RESULTS

Table 1. Baseline demographic characteristics, Completer Population N=51

Demographics	Overall (N=51) N (%)
Age, mean, years	34.4
Gender	
Male	35 (68.63%)
Female	16 (31.37%)
Race	
Black / African American	32 (62.7%)
White	14 (27.5%)
Other	5 (9.8%)
Ethnicity	
Hispanic or Latino	4 (7.8%)
Not Hispanic or Latino	47 (92.2%)

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=51	REL-1017 25 mg N=51	REL-1017 75 mg N=51	REL-1017 150 mg N=51	Dextromethorphan 300 mg N= 51	Ketamine 0.5 mg/kg N=51
Mean (SD)	50.9 (2.2)	51.4 (3.3)	54.9 (9.6)	59.2 (14.4)	68.4 (18.4)	90 (14.5)
Median	50	50	50	51	60	100
Ketamine 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	0.003		--

++ 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 ketamine was significantly greater than placebo, confirming study validity.
- The E_{max} for ketamine was greater than all 3 doses of REL-1017 (p<0.001). All REL-1017 tested doses exhibited at least a 30-point median intra-participant difference in Drug Liking E_{max} (primary endpoint) compared to ketamine.
- Comparison of REL-1017 to placebo, using the FDA suggested equivalence analysis, indicated that REL-1017 is statistically equivalent to placebo with p<0.05 at all tested doses.
- Comparison of REL-1017 to dextromethorphan indicated that REL-1017 is statistically different from dextromethorphan with p<0.05 at all tested doses. Dextromethorphan was statistically different from placebo and from ketamine p<0.05.

CONCLUSIONS

- **In this HAP study among recreational ketamine 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 ketamine .5mg/kg in Drug Liking Emax (primary endpoint) (p<0.001) in the completer population.**
- **All REL-1017 were statistically equivalent to placebo for Drug Liking E_{max} ("at this moment") (p<0.05) in the completer population.**
- **Comparable results of REL-1017 vs ketamine were observed for the two key secondary endpoints ("Overall Drug Liking" and "Take Drug Again").**
- **This study showed no meaningful ketamine-like abuse potential for REL-1017.**

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

Overall Drug Liking VAS	Placebo N=51	REL-1017 25 mg N=51	REL-1017 75 mg N=51	REL-1017 150 mg N=51	Dextromethorphan 300 mg N= 51	Ketamine 0.5 mg/kg N=51
Mean (SD)	47.7 (9.7)	51.3 (8)	50.8 (13.7)	52.9 (20.1)	57.7 (30.8)	87.4 (19.3)
Median	50	50	50	50	59	100
Ketamine vs REL-1017 (difference), p-value	<0.001	<0.001	<0.001	<0.001		--

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

Take Drug Again VAS	Placebo N=51	REL-1017 25 mg N=51	REL-1017 75 mg N=51	REL-1017 150 mg N=51	Dextromethorphan 300 mg N= 51	Ketamine 0.5 mg/kg N=51
Mean (SD)	48.8 (1.9)	50.5 (10.9)	50 (2.6)	53.5 (24.4)	55.2 (33.4)	88.2 (21.9)
Median	50	50	50	50	51	100
Ketamine vs REL-1017 (difference), p-value	<0.001	<0.001	<0.001	<0.001		--

- Statistically significant differences between all tested doses of REL-1017 and ketamine were seen for the two key secondary endpoints (see Tables 3 and 4).

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DISCLOSURES

Shram and Henningfield contributed equally. 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.

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