Abstract Text (300 word limit, now 300, excluding bolded headings)

Title (200 character limit, now 107):

REL-1017 (esmethadone) Demonstrates No Withdrawal Effects or Evidence of Physical Dependence in a Rat Study

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Purpose: REL-1017 (esmethadone) is a novel NMDA channel blocker in development for major depressive disorder (MDD). REL-1017 has twenty-fold lower affinity than levomethadone at the mu-opioid receptor. According to a 2019 DEA statement, "The d-isomer lacks significant respiratory depressant action and addiction liability, but possesses antitussive activity." We assessed the potential of REL-1017 to produce physical dependence and signs of withdrawal. The active comparators were morphine and ketamine.

Methods: Consistent with FDA's 2017 guidance, 16 Sprague-Dawley rats/group were administered saline (control group), REL-1017 (62.5 or 100 mg/kg), ketamine (200 mg/kg) or morphine (300 mg/kg) twice daily for 30 days by oral gavage. Measures related to drug administration (Days 1, 15, 30) and discontinuation effects (Days 1 to 9 after the last dose was administered) were collected including locomotor activity and functional observational batteries. Statistical analysis compared treated groups with control group.

Results: Compared to control, REL-1017 group did not demonstrate statistically significant changes in most of the withdrawal syndrome measures over the 9 days after discontinuation of daily dosing. Ketamine-treated rats showed variable differences related to increased locomotor activity (～ 15% $p<0.01$). Morphine-treated rats demonstrated significant changes in elements of cluster of signs of withdrawal of the opiate-type, including parameters of activity and arousal (increase of easy of removal scores～ 120%, increase of handling reactivity scores ～ 75%, and decrease of rearing counts～ 66%; $p<0.01$), of autonomic (increase of defecation counts～ 90%, $ps<0.05$), neuromuscular (increase of hindlimb grip strength～ 15%, $ps<0.05$) and sensorimotor (non-threatening approach response, tail pinch, and simple body-touch increase ～ 10%, $ps<0.05$) activity, as well as decreased weight (～ 14%, $p<0.01$).

Conclusions and Discussion: REL-1017 produced no evidence of physical dependence or withdrawal syndrome. This study confirms that REL-1017 does not have full opioid agonist effects and is consistent with the 2019 DEA statement on abuse liability.

Keywords: esmethadone; dextromethadone; morphine; physical dependence; withdrawal; abuse; opioid.

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him as a friend as well as a respected and invaluable colleague (see https://cpdd.org/membership/in-memoriam/).