No Indication of Abuse Potential and Absence of Withdrawal Signs and Symptoms From Esmethadone (REL-1017): Results From a Phase 3 Randomized Controlled Trial in Patients With Major Depressive Disorder

Shram M[1], Henningfield J[2], Gorodetzky C[3], De Martin S[4], Vocci F[5], Sapienza F[6], Kosten T[7], Bushnell D[8], Guidetti C[9], O'Gorman C[3], Folli F[10], Traversa S[3], Inturrisi CE[3], Manfredi PL[3], **Pappagallo M[3]**

[1]Altreos Research Partners, [2]Pinney Associates, [3]Relmada Therapeutics, Inc., [4]Department of Pharmaceutical and Pharmacological Sciences, University of Padua, [5]Friends Research Institute, [6]The Drug and Chemical Advisory Group, LLC, [7]Baylor College of Medicine, MD Anderson Cancer Center, University of Houston, Michael E. DeBakey VA Medical Center, [8]Cytel, [9]Child Neuropsychiatry Unit, Department of Neuroscience, IRCCS Bambino Gesù Pediatric Hospital, [10]Department of Health Sciences, University of Milan

No Indication of Abuse Potential and Absence of Withdrawal Signs and Symptoms From Esmethadone (REL-1017): Results From a Phase 3 Randomized Controlled Trial in Patients With Major Depressive Disorder

Aim: Esmethadone (REL-1017) is an N-methyl-D-aspartate receptor uncompetitive antagonist and antidepressant candidate with promising safety, tolerability, and efficacy results from Phase 1 and 2 trials. Given its structural similarity to methadone, the abuse and dependence potential of REL-1017 in patients with major depressive disorder (MDD) was assessed.

Methods: A Phase 3, randomized, double-blind, placebo-controlled trial was conducted in 18- to 65-year-old patients with MDD experiencing a major depressive episode despite ongoing treatment with a standard antidepressant. Patients received 75 mg REL-1017 (loading dose) or placebo once daily on Day 1 and 25 mg REL-1017 or placebo from Days 2 to 28. "Drug liking," "drug high," and "desire to take the drug again" were assessed with a 0-100 visual analogue scale (VAS). The Misuse, Abuse, and Diversion Drug Event Reporting System (MADDERS®) was used to assess potentially abuse-related events. Potential withdrawal was assessed for 14 days after treatment discontinuation (Days 28-42) using the Physician Withdrawal Checklist (PWC), Clinical Opiate Withdrawal Scale (COWS), and Subjective Opiate Withdrawal Scale (SOWS).

Results: Among 227 patients receiving any study drug (114 placebo, 113 REL-1017), adverse events (AEs) were mild or moderate and transient. There were 3 serious AEs, although none were treatment related. Placebo and REL-1017 groups showed no differences in VAS scores for "drug liking," "drug high," or "desire to take the drug again." There was no indication of abuse on the MADDERS®. Among patients who participated in the safety withdrawal assessment (97 placebo, 87 REL-1017), change from baseline on the PWC, COWS, and SOWS was slight, not clinically meaningful, and did not differ between groups.

Conclusions: No indications of abuse potential for REL-1017 were observed, and discontinuation resulted in no withdrawal signs or symptoms. These results confirmed the lack of meaningful abuse potential seen in earlier studies.

BACKGROUND

- Esmethadone (REL-1017) is an N-methyl-D-aspartate receptor (NMDAR) uncompetitive antagonist and antidepressant candidate with promising pharmacokinetic, safety, tolerability, and efficacy results from Phase 1 and 2 trials[1-3]
- While available preclinical and clinical data indicate that REL-1017 has no meaningful opioid agonist action or abuse potential, even at supratherapeutic doses,[4,5] because it is the dextro-isomer of methadone, the question of its abuse and dependence potential in MDD patients warranted further exploration

OBJECTIVES

- To assess the abuse and dependence potential of REL-1017 in patients with major depressive disorder (MDD) enrolled in a Phase 3 trial (NCT04688164) by (1) applying established measurements that could signal abuse potential and (2) assessing withdrawal effects after abrupt discontinuation

METHODS

Study Design:
- A Phase 3, randomized, double-blind, placebo-controlled trial of oral once-daily adjunctive REL-1017 was conducted in patients with MDD and inadequate response to standard antidepressants
- Patients were aged 18 to 65 years and experiencing a major depressive episode despite ongoing treatment with an adequate course of a standard antidepressant
- Patients were randomly assigned to receive 75 mg REL-1017 (loading dose) or placebo on Day 1, followed by 25 mg REL-1017 or placebo from Day 2 to Day 28
- Established measurements that could signal abuse potential were applied during the trial (Days 1-42)
- Potential withdrawal was assessed for 14 days from the last day of treatment (from Day 28 baseline until Day 42)

Measurements:
- Review of all adverse events (AEs)
- The Clinician-Administered Dissociative States Scale (CADSS)
- "Drug liking," "drug high," and "desire to take the drug again" were assessed at specific time points (Days 4, 7, 14, 21, and 28) with a 0-100 visual analogue scale (VAS)
- The Misuse, Abuse, and Diversion Drug Event Reporting System (MADDERS®) was used to assess potentially abuse-related events[6]
- Potential withdrawal was assessed for 14 days from the last day of treatment (Day 28) using the Physician Withdrawal Checklist (PWC-20), Clinical Opiate Withdrawal Scale (COWS), and Subjective Opiate Withdrawal Scale (SOWS)

RESULTS

Table 1. Treatment-emergent adverse events (TEAEs).

Variable	Placebo (N=114)		REL-1017 25 mg (N=113)		All patients (N=227)	
	N	%	N	%	N	%
Patients with ≥1 TEAE*	61	53.5	55	48.7	116	51.1
Patients with ≥1 treatment-related TEAE	28	24.6	30	26.5	58	25.6
Patients with ≥1 serious treatment-related TEAE	0	0	0	0	0	0
Patients with TEAE leading to withdrawal of study drug	5	4.4	2	1.8	7	3.1
TEAEs occurring in 5% or more of patients per treatment arm						
Headache	9	7.9	13	11.5	22	9.7
COVID-19	10	8.8	6	5.3	16	7
Upper respiratory tract infection	6	5.3	8	7.1	14	6.2
Nausea	5	4.4	8	7.1	13	5.7
Diarrhea	7	6.1	5	4.4	12	5.3
Constipation	7	6.1	3	2.7	10	4.4
Dizziness	2	1.8	7	6.2	9	4

*A TEAE is defined as an AE that starts or worsens at any time after initiation of study drug.

Table 2. CADSS scores. Day 28 was the last day of study drug treatment.

Time points	Placebo (N=114)		REL-1017 25 mg (N=113)	
	n	Mean (SD)	n	Mean (SD)
Baseline	109	1.1 (3)	110	1 (2.2)
Day 4	84	0.4 (1.5)	89	0.6 (1.3)
Day 7	108	0.5 (1.8)	109	0.5 (1.8)
Day 14	104	0.3 (1.1)	106	0.3 (1.0)
Day 21	99	0.2 (0.7)	101	0.3 (0.8)
Day 28	89	0.1 (0.4)	105	0.3 (0.8)
Day 30 (safety follow-up)	88	0.2 (0.6)	93	0.2 (0.7)
Day 32 (safety follow-up)	87	0.1 (0.3)	91	0.2 (0.9)
Day 35 (safety follow-up)	89	0.1 (0.3)	98	0.1 (0.5)
Day 42 (safety follow-up)	93	0.2 (0.6)	98	0.1 (0.6)

The CADSS is a 23-item scale, with each item scaled from 0 to 4 corresponding to the dissociative states of not at all, mild, moderate, severe, and extreme, thus resulting in a total score between 0 and 92. A higher total score indicates a higher likelihood of the presence of a dissociative state.

Table 3. VAS scores.

	Treatment time points (Days 1-28)	Placebo (N=114)		REL-1017 25 mg (N=113)	
		n	Mean (SD)	n	Mean (SD)
Do you like the drug effect you are feeling now?	Day 4	35	52.9 (24.8)	44	50.2 (25.2)
	Day 7	77	54.3 (25)	75	53.2 (28.3)
	Day 14	52	51.3 (27.4)	61	54.9 (24.5)
	Day 21	57	52.8 (27.5)	54	57.9 (26.8)
	Day 28	62	52.9 (29.4)	74	53.1 (27.4)
How high are you now?	Day 4	35	13.2 (23.9)	44	12 (23.2)
	Day 7	77	11.6 (20.7)	75	12.1 (22.2)
	Day 14	52	15.7 (25.4)	61	9.6 (21.1)
	Day 21	57	13.8 (24.7)	54	14.7 (27.1)
	Day 28	63	9.2 (19.9)	74	9.8 (23.3)
Overall, my liking for this drug is…	Day 4	35	56.3 (20.1)	44	55.8 (25.5)
	Day 7	77	59.3 (27.9)	75	58.9 (27.5)
	Day 14	52	55.9 (29.3)	61	58.7 (25.7)
	Day 21	57	54.5 (29.4)	54	62 (27.4)
	Day 28	63	54.9 (31.5)	74	59.7 (28)
Would you want to take the drug again?	Day 4	35	64.1 (24.9)	44	62.9 (28.9)
	Day 7	77	63 (32.4)	75	63.5 (28.3)
	Day 14	52	56.3 (31.4)	61	64.4 (27.1)
	Day 21	57	57.8 (31.8)	54	65.6 (29.4)
	Day 28	63	54.7 (36.4)	74	62.1 (28.2)

The VAS is a psychometric response scale. When responding to a VAS item, participants specify their level of agreement to a statement by indicating a position along a continuous line between 2 endpoints.

- AEs were predominantly mild or moderate and transient, with no treatment-related serious AEs
- There were no meaningful differences in CADSS and VAS scores between REL-1017 and placebo groups

Table 4. PWC-20 and COWS scores.

Withdrawal assessment time points (Days 1-14)	PWC-20*				COWS†			
	Placebo (N=87)		REL-1017 25 mg (N=97)		Placebo (N=87)		REL-1017 25 mg (N=97)	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Day 28 (end of treatment)	85	7 (6.5)	92	6 (5.3)	86	0.4 (0.8)	94	0.5 (1.05)
Day 2	80	5.8 (5.16)	89	4.5 (4.52)	79	0.5 (1.07)	90	0.6 (0.96)
Day 4	80	6.1 (5.68)	88	4.7 (4.81)	79	0.6 (1.19)	90	0.6 (1.16)
Day 7	81	6.9 (6.04)	95	4.9 (4.86)	80	0.6 (0.99)	95	0.6 (1.04)
Day 14	83	7.2 (5.72)	96	5.4 (4.99)	86	0.4 (0.96)	97	0.5 (0.9)

*The PWC-20 is a validated 20-item physician-rated survey that assesses the severity of potential symptoms of drug withdrawal. Items are rated on a scale from 0 to 3, with total scores ranging from 0 to 60. Larger values indicate more severe symptoms.
†The COWS is an 11-item scale with a total score ranging from 0 to 48. A total score of 5 to 12 is considered mild withdrawal, a total score of 13 to 24 is moderate, a total score of 25 to 36 is moderately severe, and a total score more than 36 is severe withdrawal.

Table 5. SOWS* scores.

Withdrawal assessment time points (Days 1-14)	Placebo (N=87)		REL-1017 25 mg (N=97)	
	n	Mean (SD)	n	Mean (SD)
Day 28 (end of treatment)	62	6.7 (6.51)	67	5.8 (5.06)
Day 1	42	4.8 (3.94)	42	3.2 (6.68)
Day 2	42	4 (3.5)	51	4.1 (7.16)
Day 3	39	4.2 (4.79)	44	4.1 (7.2)
Day 4	41	4.2 (4.81)	50	4.5 (6.38)
Day 5	38	3.5 (3.73)	38	4.4 (6.86)
Day 6	37	3.2 (3.41)	44	4.1 (6.12)
Day 7	43	3.4 (3.37)	51	3.8 (5.78)
Day 8	36	3.8 (4.8)	37	4.4 (8.29)
Day 9	31	3.1 (3.44)	32	3.5 (7.01)
Day 10	34	3.4 (3.75)	38	2.9 (6.27)
Day 11	32	2.5 (3.41)	36	3.7 (7.1)
Day 12	27	2.7 (3.67)	29	3.2 (4.92)
Day 13	33	3.2 (4.4)	33	4 (7.32)
Day 14	27	2.8 (3.45)	39	4.1 (6.48)

*The SOWS is a questionnaire in which participants self-rate how they feel about a list of withdrawal symptoms on a scale of 0 (not at all) to 4 (extremely). The total score is the sum of 16 symptom ratings and ranges from 0 to 64.

Table 6. Summary of potentially abuse-related events reviewed by the MADDERS®.

Decision type	Number of events	
Independent review*	5	
Panel decision	6	
Total cases adjudicated	11	
Category classification of events	REL-1017	Placebo
Abuse	0	0
Misuse	0	0
Suicide-related	0	0
Therapeutic error†	5 (2 pts)	2 (1 pt)
Withdrawal	0	0
None of these‡	3 (2 pts)	1 (1 pt)
Unable to classify	0	0

*MADDERS® Adjudication Committee (MAC) members independently review and adjudicate each case. If agreement is not reached during independent adjudication, the case is presented at Panel meeting for the MAC to review as a group to reach consensus.
†This refers to unintentional errors made by the prescriber or patient, such as erroneous prescription or erroneous instructions from a healthcare provider; wrong medication dispensed; subject's taking the medication not according to directions.
‡Sufficient information indicates that none of the previous categories apply (for example, misplacing pills or pill containers).

Table 7. Baseline demographic characteristics.

Demographics	Overall (N=227) N (%)
Years of age, mean (SD)	43.5 (14.6)
Montgomery-Åsberg Depression Rating Scale (MADRS) total score, mean (SD)	35 (4.8)
Body mass index (kg/m²), mean (SD)	26.026 (3.035)
Sex	
Male	58 (25.6)
Female	169 (74.4)
Race	
Asian	13 (5.7)
Black/African American	30 (13.2)
White	175 (77.1)
Multiracial	6 (2.6)
Other	3 (1.3)
Ethnicity	
Hispanic or Latino	52 (22.9)
Not Hispanic or Latino	164 (72.2)
Not reported	9 (4)
Unknown	2 (0.9)

- There were no indications of abuse-related events related to study drug as per MADDERS®
- Among patients who participated in the safety withdrawal assessment, changes from baseline on the PWC-20, COWS, and SOWS were not clinically meaningful and did not differ between groups

CONCLUSIONS

- **Among 227 patients with MDD randomized to placebo or REL-1017 for 28 days, no signals of abuse potential were observed across multiple measures**
- **Among 184 patients who participated in the safety withdrawal assessment, abrupt discontinuation resulted in no withdrawal signs or symptoms**
- **This Phase 3 trial is consistent with the favorable tolerability and safety profile of REL-1017 and the lack of meaningful abuse potential seen in earlier studies**

REFERENCES

1. Bernstein G, Davis K, Mills C, et al. Characterization of the safety and pharmacokinetic profile of D-methadone, a novel N-methyl-D-aspartate receptor antagonist in healthy, opioid-naive subjects: results of two Phase 1 studies. *J Clin Psychopharmacol.* 2019;39(3):226-237.
2. Fava M, Stahl S, Pani L, et al. REL-1017 (esmethadone) as adjunctive treatment in patients with major depressive disorder: a Phase 2a randomized double-blind trial. *Am J Psychiatry.* 2022;179(2):122-131.
3. Shram M, Henningfield J, Apseloff G, et al. The novel uncompetitive NMDA receptor antagonist esmethadone (REL-1017) has no meaningful abuse potential in recreational drug users. *Transl Psychiatry.* Forthcoming 2023.
4. Fava M, Stahl SM, De Martin S, et al. Esmethadone-HCl (REL-1017): a promising rapid antidepressant. *Eur Arch Psychiatry Clin Neurosci.* 2023;10.1007/s00406-023-01571-4.
5. Henningfield J, Gauvin D, Bifari F, et al. REL-1017 (esmethadone; D-methadone) does not cause reinforcing effect, physical dependence and withdrawal signs in Sprague Dawley rats. *Sci Rep.* 2022;12(1):11389.
6. WCG. Abuse-potential solution. Accessed April 26, 2023. https://www.wcgclinical.com/services/abuse-potential-solution

DISCLOSURES

Drs. Shram and Henningfield and Drs. Manfredi and Pappagallo contributed equally. This work was funded by Relmada Therapeutics, Inc. Drs. Shram, Henningfield, Gorodetzky, Vocci, Sapienza, Folli, Pappagallo, Manfredi, Kosten, and Inturrisi have received consultant fees from Relmada Therapeutics, Inc. Dr. De Martin is employed by or has received compensation from companies or institutions that received funding from Relmada Therapeutics, Inc. and has received grant support from MGGM LLC and consultant fees from Neuroarbor LLC. Dr. Guidetti has received consultant fees from MGGM LLC. Drs. O'Gorman and Traversa are employees of Relmada Therapeutics, Inc. Drs. Inturrisi and Manfredi are co-inventors of technology related to esmethadone.

Relmada THERAPEUTICS

Corresponding author: Marco Pappagallo, MD Email: mpappagallo@relmada.com