P.0166

No Indication of Abuse Potential and Absence of Withdrawal From Esmethadone (REL-1017) in Patients With Major Depressive Disorder

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

[1]Altreos Research Partners, [2]Relmada Therapeutics, Inc., [3]Pinney Associates, [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

INTRODUCTION

- The N-methyl-D-aspartate receptor (NMDAR) uncompetitive antagonist esmethadone (REL-1017) is an antidepressant candidate with promising pharmacokinetic, safety, tolerability, and efficacy results from Phase 1 and 2 trials [1-3]
- Available data indicate that REL-1017 has no meaningful reinforcing effects in preclinical models [4] and no meaningful abuse potential in recreational users, even at supratherapeutic doses [5]. We have now explored its potential for abuse and dependence in patients with MDD

AIM

- To assess the abuse and dependence potential of REL-1017 in patients with major depressive disorder (MDD) enrolled in two Phase 3 trials (NCT04688164 and NCT04855747) by (1) applying established measurements that could signal abuse potential [6] and (2) assessing withdrawal effects after abrupt discontinuation

METHODS

Study Design:

- Two Phase 3, randomized, double-blind, placebo-controlled trials of once-daily oral adjunctive REL-1017 were conducted in 18- to 65-year-old patients with MDD
- In study 301, REL-1017 or placebo was administered across 43 US centers as an adjunctive treatment to patients with inadequate response to standard antidepressants
- In study 303, REL-1017 or placebo was administered to patients as monotherapy across 45 US centers
- There were 20 overlapping study centers that enrolled patients in both studies, enrolling 76% of the total 227 patients in study 301 and 60% of the total 232 patients in study 303
- 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 of abuse potential were used during the trial (Days 1-42)
- Potential withdrawal was rated for 14 days from the final 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 measured at fixed time points (Days 4, 7, 14, 21, and 28) with a 0- to 100-point 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 rated for 14 days from the final 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	Study 301						Study 303					
	Placebo (N=114)		REL-1017 25 mg (N=113)		All patients (N=227)		Placebo (N=116)		REL-1017 25 mg (N=116)		All patients (N=232)	
	N	%	N	%	N	%	N	%	N	%	N	%
Patients with ≥1 TEAE*	61	53.5	55	48.7	116	51.1	56	48.3	62	53.4	118	50.9
Patients with ≥1 treatment-related TEAE	28	24.6	30	26.5	58	25.6	37	31.9	39	33.6	76	32.8
Patients with ≥1 serious treatment-related TEAE	0	0	0	0	0	0	0	0	0	0	0	0
Patients with TEAE leading to discontinuation of study drug	5	4.4	2	1.8	7	3.1	2	1.7	2	1.7	4	1.7
TEAEs occurring in 5% or more of patients per treatment arm in either study												
Headache	9	7.9	13	11.5	22	9.7	11	9.5	13	11.2	24	10.3
COVID-19	10	8.8	6	5.3	16	7.0	3	2.6	11	9.5	14	6.0
Upper respiratory tract infection	6	5.3	8	7.1	14	6.2	7	6.0	2	1.7	9	3.9
Nausea	5	4.4	8	7.1	13	5.7	6	5.2	11	9.5	17	7.3
Diarrhea	7	6.1	5	4.4	12	5.3	2	1.7	4	3.4	6	2.6
Constipation	7	6.1	3	2.7	10	4.4	5	4.3	3	2.6	8	3.4
Dizziness	2	1.8	7	6.2	9	4.0	5	4.3	10	8.6	15	6.5
Dry mouth	1	0.9	1	0.9	2	0.9	3	2.6	6	5.2	9	3.9
Fatigue	2	1.8	2	1.8	4	1.8	4	3.4	6	5.2	10	4.3

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

- AEs were transient and of predominantly mild or moderate severity
- There were no treatment-related serious AEs

Assessments of abuse potential

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

Time points	Study 301				Study 303			
	Placebo (N=114)		REL-1017 25 mg (N=113)		Placebo (N=116)		REL-1017 25 mg (N=116)	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Baseline	109	1.1 (3.0)	110	1.0 (2.2)	114	1.4 (3.2)	114	1.9 (5.2)
Day 4	84	0.4 (1.5)	89	0.6 (1.3)	87	0.9 (2.7)	82	1.2 (4.5)
Day 7	108	0.5 (1.8)	109	0.5 (1.8)	106	0.7 (2.4)	107	0.8 (3.1)
Day 14	104	0.3 (1.1)	106	0.3 (1.0)	101	0.6 (2.2)	105	0.8 (2.7)
Day 21	99	0.2 (0.7)	101	0.3 (0.8)	97	0.2 (0.8)	103	0.6 (2.3)
Day 28	89	0.1 (0.4)	105	0.3 (0.8)	99	0.2 (0.6)	104	0.4 (1.8)
Day 30 (safety follow-up)	88	0.2 (0.6)	93	0.2 (0.7)	71	0.2 (0.5)	90	0.7 (4.1)
Day 32 (safety follow-up)	87	0.1 (0.3)	91	0.2 (0.9)	69	0.2 (0.7)	91	0.6 (3.1)
Day 35 (safety follow-up)	89	0.1 (0.3)	98	0.1 (0.5)	71	0.3 (1.6)	91	0.8 (2.9)
Day 42 (safety follow-up)	93	0.2 (0.6)	98	0.1 (0.6)	80	0.6 (2.6)	92	0.6 (3.2)

The CADSS is a 23-item scale where each item is 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 that ranges from 0 to 92. A higher total score suggests a higher likelihood that there is a dissociative state.

Table 3. VAS scores.

	Treatment time points (Days 1-28)	Study 301				Study 303			
		Placebo (N=114)		REL-1017 25 mg (N=113)		Placebo (N=116)		REL-1017 25 mg (N=116)	
		n	Mean (SD)	n	Mean (SD)	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)	53	52.4 (24.5)	48	57.3 (28.5)
	Day 7	77	54.3 (25.0)	75	53.2 (28.3)	89	46.3 (28.4)	87	53.3 (27.5)
	Day 14	52	51.3 (27.4)	61	54.9 (24.5)	71	47.9 (29.9)	74	52.0 (29.6)
	Day 21	57	52.8 (27.5)	54	57.9 (26.8)	73	48.6 (28.3)	73	53.0 (29.8)
	Day 28	62	52.9 (29.4)	74	53.1 (27.4)	81	50.2 (29.8)	93	52.1 (31.4)
How high are you now?	Day 4	35	13.2 (23.9)	44	12.0 (23.2)	53	16.8 (27.5)	48	14.0 (26.0)
	Day 7	77	11.6 (20.7)	75	12.1 (22.2)	89	10.4 (20.0)	88	8.4 (18.1)
	Day 14	52	15.7 (25.4)	61	9.6 (21.1)	71	12.9 (24.0)	74	11.6 (21.8)
	Day 21	57	13.8 (24.7)	54	14.7 (27.1)	73	13.2 (23.3)	73	11.2 (21.2)
	Day 28	63	9.2 (19.9)	74	9.8 (23.3)	81	11.3 (22.0)	93	9.2 (21.4)
Overall, my liking for this drug is…	Day 4	35	56.3 (20.1)	44	55.8 (25.5)	53	54.2 (27.6)	48	60.4 (26.8)
	Day 7	77	59.3 (27.9)	75	58.9 (27.5)	89	47.5 (29.8)	88	57.8 (27.9)
	Day 14	52	55.9 (29.3)	61	58.7 (25.7)	71	49.6 (30.3)	74	57.2 (29.9)
	Day 21	57	54.5 (29.4)	54	62.0 (27.4)	73	49.4 (29.6)	73	59.3 (30.9)
	Day 28	63	54.9 (31.5)	74	59.7 (28.0)	81	53.4 (29.8)	93	56.9 (32.3)
Would you want to take the drug again?	Day 4	35	64.1 (24.9)	44	62.9 (28.9)	53	56.6 (28.5)	48	65.8 (28.1)
	Day 7	77	63.0 (32.4)	75	63.5 (28.3)	89	54.0 (31.8)	88	58.9 (31.9)
	Day 14	52	56.3 (31.4)	61	64.4 (27.1)	71	50.3 (30.5)	74	56.8 (32.5)
	Day 21	57	57.8 (31.8)	54	65.6 (29.4)	73	49.4 (31.0)	73	57.5 (32.8)
	Day 28	63	54.7 (36.4)	74	62.1 (28.2)	81	55.3 (30.6)	93	56.2 (35.6)

The VAS is a psychometric response scale. For each VAS item, participants provide their level of agreement with a statement by selecting a position along a continuous line between 2 endpoints.

- Placebo and REL-1017 groups did not differ in VAS scores for "drug liking," "drug high," or "desire to take the drug again"

Assessments of withdrawal

Table 4. PWC-20 scores.

Withdrawal assessment time points (Days 1-14)	Study 301				Study 303			
	Placebo (N=87)		REL-1017 25 mg (N=97)		Placebo (N=77)		REL-1017 25 mg (N=93)	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Day 28 (end of treatment)	85	7.0 (6.50)	92	6.0 (5.30)	74	7.0 (5.27)	91	7.1 (6.19)
Day 2	80	5.8 (5.16)	89	4.5 (4.52)	70	5.1 (4.64)	87	5.5 (5.54)
Day 4	80	6.1 (5.68)	88	4.7 (4.81)	67	5.1 (4.71)	87	6.0 (5.89)
Day 7	81	6.9 (6.04)	95	4.9 (4.86)	70	6.3 (6.17)	89	6.9 (6.08)
Day 14	83	7.2 (5.72)	96	5.4 (4.99)	74	6.5 (6.21)	90	7.4 (6.73)

The PWC-20 is a validated 20-item physician-rated survey that evaluates the severity of potential drug withdrawal symptoms. Items are rated on a scale between 0 and 3, and total scores range from 0 to 60. Larger values indicate greater symptom severity.

Table 5. COWS scores.

Withdrawal assessment time points (Days 1-14)	Study 301				Study 303			
	Placebo (N=87)		REL-1017 25 mg (N=97)		Placebo (N=77)		REL-1017 25 mg (N=93)	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Day 28 (end of treatment)	86	0.4 (0.80)	94	0.5 (1.05)	73	0.4 (0.74)	90	0.5 (1.57)
Day 2	79	0.5 (1.07)	90	0.6 (0.96)	66	0.2 (0.57)	86	0.4 (0.88)
Day 4	79	0.6 (1.19)	90	0.6 (1.16)	65	0.5 (0.90)	86	0.6 (1.04)
Day 7	80	0.6 (0.99)	95	0.6 (1.04)	69	0.5 (1.30)	89	0.6 (1.24)
Day 14	86	0.4 (0.96)	97	0.5 (0.90)	74	0.5 (1.28)	90	0.4 (0.95)

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 suggests moderate withdrawal, a total score of 25 to 36 suggests moderately severe withdrawal, and a total score above 36 suggests severe withdrawal.

Table 6. SOWS scores.

Withdrawal assessment time points (Days 1-14)	Study 301				Study 303			
	Placebo (N=87)		REL-1017 25 mg (N=97)		Placebo (N=77)		REL-1017 25 mg (N=93)	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Day 28 (end of treatment)	62	6.7 (6.51)	67	5.8 (5.06)	62	5.5 (4.67)	79	5.9 (5.26)
Day 1	42	4.8 (3.94)	42	3.2 (6.68)	38	2.9 (3.62)	49	2.7 (3.34)
Day 2	42	4.0 (3.50)	51	4.1 (7.16)	43	2.9 (4.12)	55	3.5 (5.15)
Day 3	39	4.2 (4.79)	44	4.1 (7.20)	44	3.7 (4.45)	52	3.6 (5.14)
Day 4	41	4.2 (4.81)	50	4.5 (6.38)	41	2.9 (3.73)	54	3.8 (5.37)
Day 5	38	3.5 (3.73)	38	4.4 (6.86)	44	2.7 (3.45)	53	3.8 (5.44)
Day 6	37	3.2 (3.41)	44	4.1 (6.12)	48	2.6 (3.49)	55	3.3 (5.10)
Day 7	43	3.4 (3.37)	51	3.8 (5.78)	48	3.6 (4.63)	55	2.9 (4.10)
Day 8	36	3.8 (4.80)	37	4.4 (8.29)	44	3.0 (4.43)	53	2.7 (4.56)
Day 9	31	3.1 (3.44)	32	3.5 (7.01)	41	3.0 (4.07)	49	2.5 (4.61)
Day 10	34	3.4 (3.75)	38	2.9 (6.27)	41	3.0 (4.11)	46	2.9 (4.73)
Day 11	32	2.5 (3.41)	36	3.7 (7.10)	38	2.5 (3.40)	42	2.8 (5.35)
Day 12	27	2.7 (3.67)	29	3.2 (4.92)	40	2.9 (3.89)	45	(3.4) (6.37)
Day 13	33	3.2 (4.40)	33	4.0 (7.32)	40	2.3 (3.19)	44	3.0 (6.37)
Day 14	27	2.8 (3.45)	39	4.1 (6.48)	40	3.3 (4.89)	52	3.0 (5.38)

The SOWS is a 16-item self-rated questionnaire that assesses how participants feel about a list of withdrawal symptoms on a scale 0 (not at all) to 4 (extremely). The total score is the sum of the 16 ratings and ranges from 0 to 64.

- There was a slight change from baseline on the PWC-20, COWS, and SOWS that was not clinically meaningful and lacked between-group differences at each time point

Table 7. 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 there is no agreement reached during independent adjudication, then the case goes to Panel meeting for MAC to review as a group and reach consensus.
†Refers to unintentional prescriber or patient errors, such as erroneous prescription or erroneous instructions from a healthcare provider; incorrect medication dispensed; patient not taking the medication according to directions.
‡Sufficient information reveals that none of the previous categories apply (eg, misplacing pills or pill containers).

- There were no indications of abuse-related events related to study drug as per MADDERS®

Table 8. Baseline demographic characteristics.

	Study 301	Study 303
Demographics	Overall (N=227) N (%)	Overall (N=232) N (%)
Years of age, mean (SD)	43.5 (14.6)	37.4 (13.0)
Montgomery-Åsberg Depression Rating Scale (MADRS) total score, mean (SD)	35 (4.8)	35.3 (4.5)
Body mass index (kg/m^2), mean (SD)	26.026 (3.035)	25.248 (3.250)
Sex		
Male	58 (25.6)	78 (33.6)
Female	169 (74.4)	154 (66.4)
Race		
Asian	13 (5.7)	14 (6.0)
Black/African American	30 (13.2)	43 (18.5)
White	175 (77.1)	165 (71.1)
Multiracial	6 (2.6)	6 (2.6)
Other	3 (1.3)	4 (1.7)
Ethnicity		
Hispanic or Latino	52 (22.9)	82 (35.3)
Not Hispanic or Latino	164 (72.2)	146 (62.9)
Not reported	9 (4)	4 (1.7)
Unknown	2 (0.9)	0 (0.0)

CONCLUSIONS

- **Among 459 patients across 2 studies who received either placebo or REL-1017, there were no indications of abuse potential as assessed using multiple measures**
  - **AEs were mild or moderate and transient, and there were no treatment-related serious AEs**
- **Across the 354 patients taken from both studies who participated in the safety withdrawal assessment, abrupt discontinuation was not associated with withdrawal signs or symptoms**
- **These Phase 3 trials are consistent with the favorable tolerability and safety profile and the lack of meaningful abuse potential observed for REL-1017 in prior studies**

REFERENCES

[1] Bernstein, G., Davis, K., Mills, C., Wang, L., McDonnell, M., Oldenhof, J., Inturrisi, C., Manfredi, P.L., Vitolo, O.V., 2019. 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. 39(3), 226-237.

[2] Fava, M., Stahl, S., Pani, L., De Martin, S., Pappagallo, M., Guidetti, C., Alimonti, A., Bettini, E., Mangano, R.M., Wessel, T., de Somer, M., Caron, J., Vitolo, O.V., DiGuglielmo, G.R., Gilbert, A., Mehta, H., Kearney, M., Mattarei, A., Gentilucci, M., Folli, F., Traversa, S., Inturrisi, C.E., Manfredi, P.L., 2022. REL-1017 (esmethadone) as adjunctive treatment in patients with major depressive disorder: a Phase 2a randomized double-blind trial. Am. J. Psychiatry 179(2), 122-131.

[3] Fava, M., Stahl, S.M., De Martin, S., Mattarei, A., Bettini, E., Comai, S., Alimonti, A., Bifari, F., Pani, L., Folli, F., Guidetti, C., Furlan, A., Sgrignani, J., Locatelli, P., Cavalli, A., O'Gorman, C., Traversa, S., Inturrisi, C.E., Pappagallo, M., Manfredi, P.L., 2023. Esmethadone-HCl (REL-1017): a promising rapid antidepressant. Eur. Arch. Psychiatry Clin. Neurosci. 10.1007/s00406-023-01571-4.

[4] Henningfield, J., Gauvin, D., Bifari, F., Fant, R., Shram, M., Buchhalter, A., Ashworth, J., Lanier, R., Pappagallo, M., Inturrisi, C., Folli, F., Traversa, S., Manfredi, P.L., 2022. REL-1017 (esmethadone; D-methadone) does not cause reinforcing effect, physical dependence and withdrawal signs in Sprague Dawley rats. Sci. Rep. 12(1), 11389.

[5] Shram, M., Henningfield, J., Apseloff, G., Gorodetzky, C., De Martin, S., Vocci, F., Sapienza, F., Kosten, T., Huston, J., Buchhalter, A., Ashworth, J., Lanier, R., Folli, F., Mattarei, A., Guidetti, C., Comai, S., O'Gorman, C., Traversa, S., Inturrisi, C., Manfredi, P.L., Pappagallo, M., 2023. The novel uncompetitive NMDA receptor antagonist esmethadone (REL-1017) has no meaningful abuse potential in recreational drug users. Transl. Psychiatry 13(1), 192.

[6] WCG. Abuse-potential solution. Available from: https://www.wcgclinical.com/services/abuse-potential-solution. [Accessed: 26 April 2023].

DISCLOSURES

Drs. Shram, Pappagallo, and Henningfield 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.

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