Esmethadone (REL-1017) in Patients With Major Depressive Disorder and Antidepressant Tachyphylaxis:

An Exploratory Post Hoc Analysis From a Phase 3 Randomized Controlled Trial

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Abstract

Background: Antidepressant tolerance/tachyphylaxis (AT) is defined as initial response (≥ 50% improvement) to antidepressant treatment followed by relapse while on the same adequate dose. The impact of AT as prognostic indicator for response to subsequent antidepressant treatment is unknown.

Objective: To test the efficacy of esmethadone (REL-1017) in a subgroup of patients with major depressive disorder (MDD) and AT.

Methods: A phase 3, double-blind, randomized, placebo-controlled trial of esmethadone was conducted in adult outpatients with MDD. Prior to randomization, AT was independently assessed by clinicians from the Massachusetts General Hospital Clinical Trials Network and Institute using the MGH Antidepressant Treatment Response Questionnaire. Data for the primary efficacy end point were analyzed using mean difference in Montgomery-Åsberg Depression Rating Scale (MADRS) total score from baseline to primary end point (Day 28) in the AT subgroup from the intent to treat (ITT) population, the per-protocol (PP) population, and in patients with severe depression (baseline MADRS ≥35).

Results: Among 227 ITT patients, 87 experienced AT. For this subgroup, there was a nominally statistically significant mean difference of 5.4 ($P = .023$, Cohen effect size 0.53) for esmethadone vs placebo in MADRS total score change from baseline to primary end point (Day 28). Additionally, there was a nominally statistically significant difference in response rate ($P = .0004$). Consistent results were seen in the PP population with AT and in the severely depressed subgroup of patients with AT.

Conclusions: These post hoc analyses, based on data collected independently pre-randomization, suggest that esmethadone may be an effective adjunctive treatment for patients with AT. These results need to be confirmed in larger prospective clinical trials.

J Clin Psychiatry 2025;86(4):24m15748

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Major depressive disorder (MDD) is a recurrent episodic disorder, where each major depressive episode (MDE) increases the probability of developing a new episode.[1] Even after the recent introduction of *N*-methyl-D-aspartate receptor (NMDAR) antagonist antidepressants, monoaminergic drugs remain the most commonly prescribed antidepressants. However, it is estimated that more than 50% of patients with MDD may develop a tolerance to monoaminergic drugs.[2,3] Antidepressant tolerance, also known as antidepressant tachyphylaxis (AT), is defined as an initial response to an adequate dose of a standard antidepressant (≥50% improvement), with subsequent loss of efficacy while on the same adequate dose.[4,5]

While the mechanism of AT is unclear and may not be the same among different patients, it is hypothesized that central nervous system synaptic receptor adaptation in response to serotonergic therapy may reverse the initial antidepressant effects.[6,7] Some studies have suggested that the risk of AT may vary depending on the class of antidepressant drug used.[8–10] In particular, selective serotonin reuptake inhibitors (SSRIs) have been associated with higher incidence of AT.[8–11] Nonselective monoamine reuptake inhibitors, such as venlafaxine and

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Clinical Points

- More than 50% of patients with major depressive disorder (MDD) do not respond to standard antidepressants. Antidepressant tachyphylaxis (AT) may be pivotal to the observed high rates of antidepressant treatment failure. More outcome data on the subgroup of MDD patients with AT are needed.
- Esmethadone may be a potentially safe and effective adjunctive treatment for patients with MDD and AT. Larger studies, adequately powered for prespecified efficacy outcomes in the subgroup of patients with AT, are needed to confirm the efficacy of esmethadone as adjunctive treatment in patients with AT.

tricyclic antidepressants (TCAs), targeting more than one neurotransmitter system, may be less likely to cause AT, and some studies have shown lower rates of AT in venlafaxine and TCA trials.[8,10,11] Potential mechanisms underlying AT, among others,[12] may also include unspecified genetic predisposition.[13,14] Moreover, having a greater genetic predisposition toward MDD is also associated with increased risk of depression recurrence.[15]

Regardless of the underlying mechanism,[4,6,7,12] AT represents a significant problem for patients suffering from MDD because their poor response to subsequent antidepressant drugs leaves them with limited treatment options. Even though some clinical trials have shown the efficacy of a dose increase as a treatment of AT,[4,16,17] most MDD clinical trials fail to address AT in reporting outcomes, making it impossible to evaluate the impact of AT on treatment effect. There is limited research about specific treatment strategies for patients with AT. The treatment options are those employed for patients who relapse and for patients with TRD and include dose increase, switch to a different drug, and augmentation with an adjunctive drug.[4,16,17]

Therefore, the development of novel treatments for MDD patients experiencing AT remains an unmet medical need. The path forward for MDD research might incorporate AT as an adequately powered prespecified study outcome.

The efficacy of uncompetitive NMDAR antagonists for the treatment of MDD was confirmed by the US Food and Drug Administration (FDA) approval of esketamine for treatment-resistant depression and for MDD with suicidal ideation. Esketamine was followed by a second NMDAR antagonist antidepressant, the combination of bupropion-dextromethorphan, which is FDA approved for MDD. Esmethadone (REL-1017) is a well-tolerated oral, once daily, NMDAR antagonist antidepressant candidate, free from metabolic, sexual, and neurological side effects[18–25] with potential advantages over currently approved adjunctive antidepressant drugs.[26–28] In the current study, we performed post hoc exploratory analyses to explore the efficacy of esmethadone as an adjunctive treatment in patients with MDD and AT. These analyses utilized data from a phase 3 randomized clinical trial of esmethadone as an adjunctive treatment in patients with MDD.[22] The parent study upon which the current paper is based did not reach statistical significance in its primary outcome. However, near nominally statistically significant results were seen in the prespecified per-protocol (PP) supportive analysis ($P = .051$), in the key secondary end point of response rate ($P = .044$), and in the exploratory post hoc analysis of the severely depressed (baseline Montgomery-Åsberg Depression Rating Scale [MADRS] ≥35) subgroup ($P = .006$).[22] It is within this context that the present post hoc exploratory study was undertaken as a hypothesis-generating, rather than hypothesis-testing, endeavor.

METHODS

Study procedures and inclusion and exclusion criteria are detailed by Fava and colleagues.[22] The trial is registered at ClinicalTrials.gov (NCT04688164). This multicenter trial was conducted in the United States in accordance with the International Council on Harmonization guidelines for Good Clinical Practice, the principles of the Declaration of Helsinki, and all regulatory requirements. The study protocol was reviewed and approved by an institutional review board, and written informed consent was obtained from all participants after receiving a complete description of the study and prior to any study procedure. This phase 3, double-blind, randomized, placebo-controlled trial of oral once-daily esmethadone administered as adjunctive treatment to the current antidepressant was conducted in adult outpatients with MDD and inadequate response to 1 to 3 antidepressants in the current MDE. Patients were 18 to 65 years old and randomly assigned to receive esmethadone (75 mg loading dose on Day 1 and then 25 mg/day thereafter) or placebo for 28 days. During screening and prior to randomization, the occurrence of AT was independently assessed by clinicians from the Massachusetts General Hospital Clinical Trials Network and Institute (MGH CTNI) using the MGH Antidepressant Treatment Response Questionnaire (ATRQ).[29] The MGH-ATRQ is used to determine the adequacy (dose and duration) of antidepressant treatment, the presence of tachyphylaxis, and the presence of treatment resistance in patients with MDD. The MGH-ATRQ defines 6 weeks of antidepressant therapy as a trial of adequate duration.[30] The ATRQ provides specific criteria for adequate dosage for the most commonly used antidepressants.[30] AT was defined as an initial response to an antidepressant (≥50% improvement),

with subsequent loss of efficacy while on the same adequate dose.[5,30] Patients were classified as having AT if they had previously responded to an antidepressant and subsequently experienced a loss of response based on patient self-report and clinician verification, including medical history and treatment records documenting prior efficacy and subsequent loss of therapeutic response. Loss of response was confirmed at the CTNI interview if the Hamilton Depression Rating Scale score was ≥17. Study eligibility was confirmed if baseline MADRS was ≥24. The intent to treat (ITT) population comprises all randomized patients. The PP population, prespecified predatabase lock as the population for supportive efficacy analyses, comprises patients completing the protocol without major protocol deviations impacting efficacy assessments. The subgroup of patients with severe depression was defined post hoc by baseline MADRS score ≥35.

We repeated the analyses detailed by Fava and colleagues[22] in the subgroup of patients who experienced AT. Matching the analyses by Fava and colleagues,[22] data were analyzed by using mean difference (MD) in MADRS total score change from baseline (CFB) to primary end point (Day 28) and by using a mixed model of repeated measures (MMRM). For MD analyses, only patients with no missing values at baseline and at Day 28 were included; for MMRM analyses, all patients were included. Analyses of patients with AT, including the determinations of remission and response rates, were performed in the ITT population and in the PP population. Additionally, based on the results from the study by Fava and colleagues,[22] which showed efficacy of esmethadone in post hoc analyses of severely depressed patients (baseline MADRS ≥35), we also analyzed the subgroup of patients with AT and severe depression.

RESULTS

ITT study population characteristics are detailed by Fava and colleagues.[22] Within the ITT population, 87 patients experienced AT. Among the 87 AT patients, 77 were included in the MD AT-ITT analysis (8 placebo subjects and 2 subjects treated with esmethadone had missing values at Day 28). Characteristics for the AT subgroup are shown in Table 1. For the primary end point (Day 28) in the AT-ITT subgroup, mean (SD) CFB to Day 28 for the MADRS total score was 12.0 (SD 9.5) for placebo (n = 33) and 17.3 (10.5) for esmethadone (n = 44) with a MD of 5.4, which was nominally statistically significant (P = .023; Cohen effect size [ES] 0.53) (Table 2; Figure 1). Response rate at primary end point (Day 28) was 19.5% with placebo and 56.5% with esmethadone (MD: 37.0%, 95% CI, 18.2 to 55.8; P = .0004; odds ratio: 5.36, 95% CI, 1.87 to 16.20) (Figure 2). Remission rate at Day 28 was 12.2% with placebo and 28.3 % with esmethadone (MD: 16.1%, 95% CI, −0.4 to 32.5; P = .064; odds ratio: 2.84, 95% CI, 0.82 to 11.17). In the AT-PP subgroup, 79 patients experienced AT, and 74 were included in the analysis (4 placebo subjects and 1 subject treated with esmethadone had missing values at Day 28). For the primary end point (Day 28) in the AT-PP subgroup, mean (SD) CFB for the MADRS total score at Day 28 was 11.4 (9.0) for placebo (n = 32) and 17.5 (10.4) for esmethadone (n = 42), with a MD of 6.1, which was nominally statistically significant (P = .010; ES = 0.62) (Supplementary Figure 1). AT-PP response rate at primary end point (Day 28) was 19.4% with placebo and 58.1% with esmethadone (MD: 38.7%, 95% CI, 19.1 to 58.3; P = .0005; odds ratio: 5.75, 95% CI, 1.88 to 18.74). Remission rate at Day 28 was 11.1% with placebo and 27.9 % with esmethadone (MD: 16.8%, 95% CI, −0.1 to 33.7; P = .064; odds ratio: 3.10, 95% CI, 0.81 to 14.42). Results from MMRM analyses for AT subgroup from the ITT and PP populations for CFB to Day 28 are shown in Supplementary Table 1.

In the subgroup of patients with severe depression (baseline MADRS ≥35), the MD (SD) CFB to Day 28 for the MADRS total score was 11.3 (9.7) for placebo (n = 20) and 20.1 (12.7) for esmethadone (n = 23), with an MD of 8.8, which was nominally statistically significant (P = .018: ES = 0.77).

DISCUSSION

Approximately 50%–60% of patients with MDD do not obtain adequate response following the first antidepressant treatment.[2] These patients are left with few satisfactory therapeutic options, especially if they fall into the category of AT.[3] Currently available adjunctive treatments for MDD unresponsive to first-line antidepressants have limited efficacy and are potentially associated with severe metabolic, neurological, and sexual side effects.[26–28] In the current subgroup analyses, esmethadone meaningfully improved depressive symptoms at primary end point in patients experiencing antidepressant tachyphylaxis (AT). The favorable efficacy outcomes observed in the AT-ITT subgroup were supported by findings in the AT-PP subgroup and in the subgroup of patients with severe depression and AT.

The efficacy of esmethadone in these subpopulations may be due to its NMDAR antagonist antidepressant mechanism of action.[31] A complementary hypothesis is that esmethadone may reverse AT via its NMDAR antagonism with a mechanism similar to the reversal of opioid tolerance.[32] In fact, esmethadone has been

Table 1.

Demographic and Baseline MADRS Characteristics for AT-ITT Subgroup With No Missing Values at Baseline and at Day 28

	All patients (N = 77)	Esmethadone (N = 44)	Placebo (N = 33)
Age, mean (SD), y	43.5 (14.3)	42.5 (14.0)	44.6 (14.8)
Female, %	71	66	79
MADRS baseline, mean (SD)	34.8 (5.0)	34.8 (5.0)	34.8 (4.60)

Abbreviations: AT-ITT = antidepressant tachyphylaxis–intent to treat, MADRS = Montgomery-Asberg Depression Rating Scale.

Table 2.

Mean Difference (MD) Change From Baseline Analyses for Placebo and for Esmethadone (REL-1017) in the AT-ITT Subgroup and in the AT-PP Subgroup at Primary End Point (Day 28)

	Placebo	Esmethadone	Mean difference (esmethadone – placebo)
Intent to treat	N = 33	N = 44	
Value at Day 28, mean (SD)	12.0 (9.5)	17.3 (10.5)	5.4 (10.1)
Median	12.0	18.0	
Interquartile range	12.0	15.0	
Min; max	31; 5	41; 3	
***P* value**			.023
Effect size			0.53
Per-protocol	N = 32	N = 42	
Value at Day 28, mean (SD)	11.4 (9.0)	17.5 (10.4)	6.1 (9.8)
Median	10.5	18.0	
Interquartile range	11.0	13.0	
Min; max	31; 5	41; 3	
***P* value**			.010
Effect size			0.62

Abbreviations: AT-ITT = antidepressant tachyphylaxis–intent to treat, AT-PP = antidepressant tachyphylaxis–per protocol.

found to enhance 5-HT–induced excitatory postsynaptic currents in experimental models of depressive-like behavior.[33] Furthermore, SSRIs bind to TrkB neurotrophin receptors and facilitate the activity of brain-derived neurotrophic factor (BDNF) at this receptor; this effect may be independent of serotonergic effects and thus independent from the development of tolerance to these effects.[34] Esmethadone has been shown to enhance neuroplasticity via a BDNF-dependent mechanism[23] and has been found to increase BDNF in humans.[35] Therefore, it is conceivable that esmethadone may work synergistically with SSRIs on increasing BDNF-mediated neural plasticity despite the presence of AT.

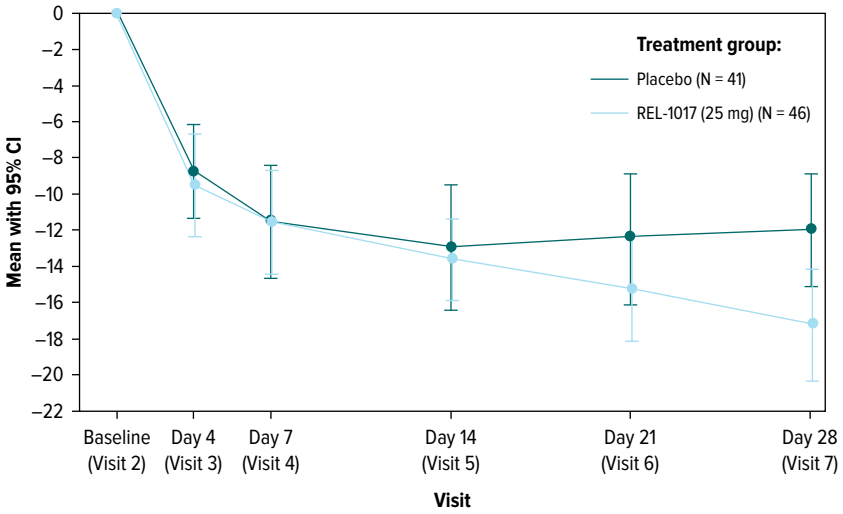
Furthermore, the antidepressant effects of esmethadone were also noted in the subgroup of patients with AT and severe depression. Given that both severely depressed patients and AT patients typically experience less favorable treatment outcomes, these findings suggest that esmethadone may be particularly effective in patients at higher risk of poor response to subsequent treatments.

Another possible explanation for the efficacy of esmethadone in patients with AT is that MDD history in these subgroups may have been better substantiated during the careful assessment performed by the independent group of specialized MGH CTNI clinicians with the use of the validated MGH ATRQ screening tool. The MGH ATRQ selection of AT patients may have selected patients with a better substantiated MDD diagnosis and screened out subjects less likely to show a treatment response to esmethadone, leading to a lower proportion of such patients in the AT subgroup. The inclusion of inappropriate study subjects is a potential cause of failed studies.[36,37]

There is an unmet need for novel treatments for patients unresponsive to standard antidepressants who are at higher risk for subsequent treatment failure, such as patients with AT, especially if they remain with severe depression.

Figure 1.

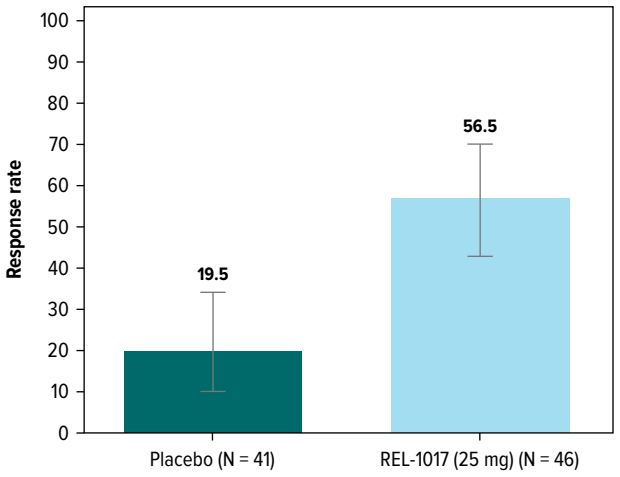
Mean Difference (MD) Change From Baseline in MADRS Total Score Over Time for Placebo and for Esmethadone (REL-1017) in the Subgroup Analysis of AT-ITT



Abbreviations: AT-ITT = antidepressant tachyphylaxis–intent to treat, MADRS = Montgomery-Asberg Depression Rating Scale.

Figure 2.

Response Rate (≥50% MADRS Reduction) at Day 28 for Placebo and for Esmethadone (REL-1017) in the Subgroup Analysis of AT-ITT



Abbreviations: AT-ITT = antidepressant tachyphylaxis–intent to treat, MADRS = Montgomery-Asberg Depression Rating Scale.

While the assessment of AT was performed at screening prior to randomization by independent clinicians from MGH CTNI, the favorable results seen in these post hoc exploratory analyses carry the risk of Type 1 statistical error due to multiple comparisons. These results need to be confirmed in future larger studies of esmethadone that are adequately powered for prespecified efficacy outcomes in the subgroup of patients with AT.

CONCLUSION

The impact of AT as a prognostic indicator for response to subsequent antidepressant treatment is unknown. Future studies might benefit from incorporating in their a priori design methodologies the possible utility of prior antidepressant tolerance/tachyphylaxis as a potentially relevant outcome moderator.

Article Information

Published Online: October 6, 2025. https://doi.org/10.4088/JCP.24m15748

Submitted: December 8, 2025; accepted August 19, 2025.

To Cite: Guidetti C, Papakostas GI, Pani L, et al. Esmethadone (REL-1017) in patients with major depressive disorder and antidepressant tachyphylaxis: an exploratory post hoc analysis from a phase 3 randomized controlled trial. *J Clin Psychiatry* 2025;86(4): 24m15748.

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Montreal, Quebec, Canada (Comai); Department of Health Sciences, University of Milan, Milan, Italy (Folli); MGGM Therapeutics, Kerhonkson, New York (Pappagallo, Manfredi).

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Relevant Financial Relationships: Drs Apicella, Champasa, Comai, De Martin, Folli, Guidetti, Kröger, Maletic, Mattarei, Manfredi, Pani, Pappagallo, and **Serra** received compensation from Relmada Therapeutics and or companies or institutions that received funding from Relmada Therapeutics, Inc. and or MGGM Therapeutics. **Dr Fava** is a consultant to Relmada on behalf of Massachusetts General Hospital and did not receive any personal compensation. **Dr Papakostas** is a consultant to Relmada on behalf of Massachusetts General Hospital and did not receive any personal compensation. **Dr Manfredi** is co-inventor and co-owner of technology related to esmethadone. **Additional disclosures: Dr Pani**: Last 2 years: consultancy: AbbVie, USA; Acumen, USA; Aicure, USA; Alexion, Italy and USA; BCG, Switzerland and Spain; Astra-Zeneca, Italy; Boehringer Ingelheim International GmbH, Germany; EDRA-LSWR Publishing Company, Italy; GH-Pharma, Ireland; GLG-Institute, USA; Immunogen, USA; Johnson & Johnson USA; LB-Pharmaceuticals, USA; Lundbeck, Denmark and Italy; Magdalena BioSciences, USA; MSD, Italy; NapoPharma, USA and EU; NetraMark, Canada; Pfizer Global, USA; RAIN Scientific, USA*; Relmada Therapeutics, USA; Takeda, USA, shares/options: Relmada USA; NetraMark Canada; RAIN Scientific USA. **Dr Fava** reports 3-year disclosures as follows: research support: Acadia Pharmaceuticals; Aditum Bio Management Company, LLC; Allergan, Alkermes, Inc; Altimate Health Corporation; Alto Neuroscience, Inc; Ancora Bio, Inc; Angelini S.p.A; Aptinyx; Arbor Pharmaceuticals LLC; Avanir Pharmaceuticals Inc; Axsome; Benckiser Pharmaceuticals, Inc; BioClinica, Inc; Biogen; BioHaven; BioShin Limited; Cambridge Science Corporation; Centrexion Therapeutics Corporation; Cerecor; Cybin IRL Limited; Eliem Therapeutics LTD; Gate Neurosciences, Inc; GenOmind, LLC; Gentelon, LLC; Happify; Johnson & Johnson; Lundbeck Inc; Marinus Pharmaceuticals; Methylation Sciences, Inc; Millennium Pharmaceutics, Inc; Minerva Neurosciences; Neuralstem; Neurocrine Biosciences, Inc; NeuroRX Inc; Novaremed; Novartis; Otsuka; Pfizer; Premiere Research International; Praxis Precision Medicines; Protagenic Therapeutics, Inc.; Relmada Therapeutics Inc; Reckitt; Shenox Pharmaceuticals; Stanley Medical Research Institute (SMRI); Taisho; Takeda; University of Michigan; Vistagen; WinSanTor, Inc; Xenon Pharmaceuticals, Inc.; National Institute of Drug Abuse (NIDA); National Institutes of Health (NIH); National Institute of Mental Health (NIMH); and PCORI. Dr. Fava has not done any personal consulting. Any consulting he has done has been on behalf of Massachusetts General Hospital, except for Sensorium Therapeutics. Speaking/publishing: Lecture given at Global Medical Education, Inc. Mood Disorders Summit, November 2020. Stock/Other Financial Options: Equity Holdings: Compellis; Neuromity; Psy Therapeutics; Sensorium Therapeutics Royalty/patent, other income: Patents for Sequential Parallel Comparison Design (SPCD), licensed by MGH to Pharmaceutical Product Development, LLC (PPD) (US_7840419, US_7647235, US_7983936, US_8145504, US_8145505); and patent application for a combination of ketamine plus scopolamine in major depressive disorder (MDD), licensed by MGH to Biohaven. Patents for pharmacogenomics of depression treatment with folate (US_9546401, US_9540691). 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All lifetime disclosures can be viewed online by navigating to https://mghcme.org/faculty > Maurizio Fava, MD > View Bio > View Disclosures Here. **Dr Papakostas** has served as a consultant for Abbott Laboratories, Acadia Pharmaceuticals, Inc*, Alkermes, Inc, Almatica*, Alphasigma USA*, Inc, AstraZeneca PLC, Arrivo Bioventures-Sirtsei Phamaceuticals, Avanir Pharmaceuticals, Axsome Therapeutics*, Boehringer Ingelheim, Boston Pharmaceuticals, Inc*, Brainsway Ltd, Bristol-Myers Squibb Company, Cala Health*, Cephalon Inc, Dey Pharma, L.P., Eleusis health solutions ltd*, Eli Lilly Co, Genentech, Inc*, Genomind, Inc*, GlaxoSmithKline, Evotec AG, H. Lundbeck A/S, Inflabloc Pharmaceuticals, Janssen Global Services LLC*, Jazz Pharmaceuticals, Johnson & Johnson Companies*, Merck*, Methylation Sciences Inc, Monopteros Therapeutics*, Mylan Inc*, Neurocenria, Novartis Pharma AG, One Carbon Therapeutics, Inc*, Osmotica Pharmaceutical Corp.*, Otsuka Pharmaceuticals, PAMLAB LLC, Pfizer Inc, Pierre Fabre Laboratories, Praxis Precision Medicines*, Ridge Diagnostics (formerly known as Precision Human Biolaboratories), Sage Therapeutics*, Shire Pharmaceuticals, Sunovion Pharmaceuticals, Taisho Pharmaceutical Co, Ltd*, Takeda Pharmaceutical Company LTD, Theracos, Inc, and Wyeth, Inc. Dr Papakostas has received honoraria (for lectures or consultancy) from Abbott Laboratories, Abbvie, Acadia Pharmaceuticals Inc, Alkermes Inc, Alphasigma USA Inc, Asopharma America Cntral Y Caribe, Astra Zeneca PLC, Avanir Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb Company, Brainsway Ltd, Cephalon Inc, Dey Pharma, L.P., Eli Lilly Co, Evotec AG, Forest Pharmaceuticals, GlaxoSmithKline, Inflabloc Pharmaceuticals, Grunbiotics Pty LTD, Hypera S.A., Jazz Pharmaceuticals, H. Lundbeck A/S, Medichem Pharmaceuticals, Inc, Meiji Seika Pharma Co Ltd, Novartis Pharma AG, Otsuka Pharmaceuticals, PAMLAB LLC, Pfizer, Pharma Trade SAS, Pierre Fabre Laboratories, Ridge Diagnostics, Shire Pharmaceuticals, Sunovion Pharmaceuticals, Takeda Pharmaceutical Company LTD, Theracos, Inc, Titan Pharmaceuticals, and Wyeth Inc. Dr Papakostas has received research support (paid to hospital) from Alphasigma USA, Inc, AstraZeneca PLC, Beckley Psytech, Bristol-Myers Squibb Company, Cala Health, Forest Pharmaceuticals, the National Institute of Mental Health, Mylan Inc, Neuralstem, Inc*, PAMLAB LLC, PCORI, Pfizer Inc, Johnson & Johnson Companies, Ridge Diagnostics (formerly known as Precision Human Biolaboratories), Sunovion Pharmaceuticals, Tal Medical, and Theracos, Inc. Dr Papakostas has served (not currently) on the speaker's bureau for Bristol Myers Squibb Co and Pfizer, Inc. *Asterisk denotes consulting activity undertaken on behalf of Massachusetts General Hospital.

Funding/Support: Relmada Therapeutics, Inc, Coral Gables, Florida, funded study REL-1017-301 (Fava 2024). This report of post hoc analyses of data from study REL-1017-301 did not receive support.

Role of the Sponsor: The views expressed in the manuscript are the authors' own and do not represent those of the former developer of the experimental drug REL-1017, Relmada Therapeutics. Inc.

Previous Presentation: Efficacy of esmethadone (REL-1017) in patients with major depressive disorder and antidepressant tolerance (antidepressant tachyphylaxis). Poster presented at the 2023 European College of Neuropsychopharmacology (ECNP) Meeting; Barcelona, Spain.

Acknowledgment: Vladimir Maletic, MD, died December 11, 2024, during the preparation of this manuscript. We honor his memory, and we wish to acknowledge his substantial contributions to this work.

Supplementary Material: Available at Psychiatrist.com.

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The Journal of Clinical Psychiatry

Supplementary Material

Article Title: Esmethadone (REL-1017) in Patients with Major Depressive Disorder and Antidepressant Tachyphylaxis: An Exploratory Post Hoc Analysis from a Phase 3 Randomized Controlled Trial

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DOI Number: 10.4088/JCP.24m15748

LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

1. **Figure 1** Mean Difference (MD) Change From Baseline in MADRS Total Score Over Time for Placebo and for Esmethadone (REL-1017) in the Subgroup Analysis of ATPP

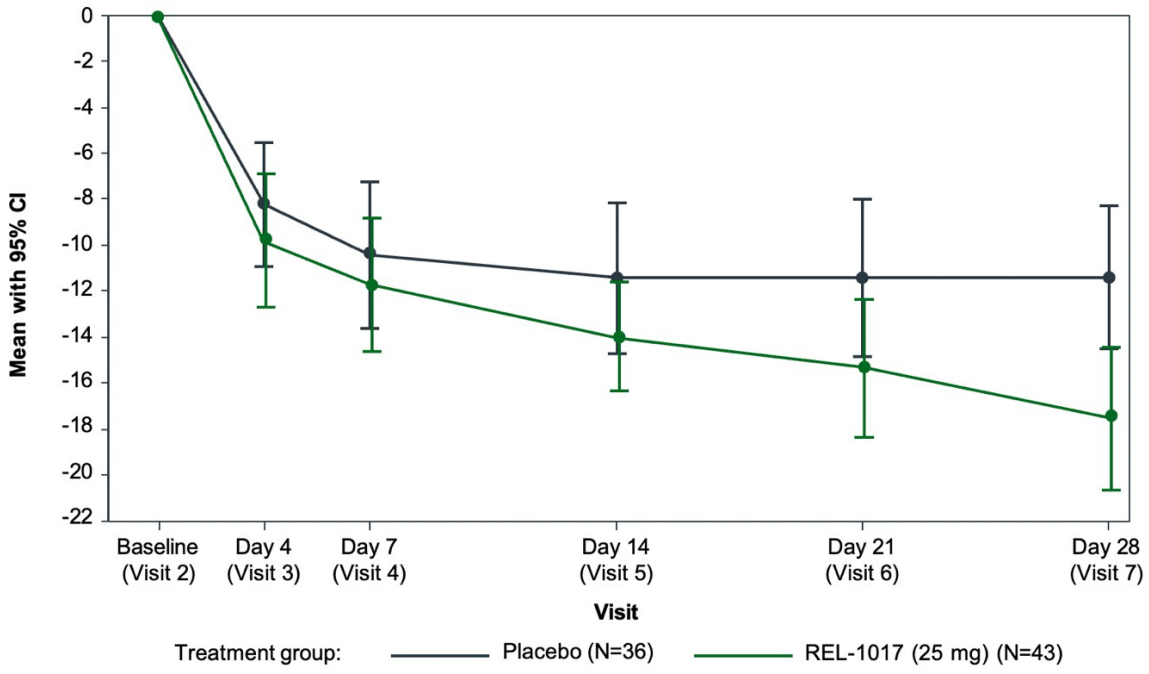
2. **Table 1** Mixed Model for Repeated Measures (MMRM) Analyses for Placebo and for Esmethadone (REL-1017) for AT-ITT Subgroup and for AT-PP Subgroup at Primary Endpoint (Day 28)

DISCLAIMER

This Supplementary Material has been provided by the authors as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplemental Figures and Tables

Supplementary Figure 1. Mean difference (MD) change from baseline in MADRS total score over time for placebo and for esmethadone (REL-1017) in the subgroup analysis of AT-PP.



Supplementary Table 1. Mixed model for repeated measures (MMRM) analyses for placebo and for esmethadone (REL-1017) for AT-ITT subgroup and for AT-PP subgroup at primary endpoint (Day 28).

	Placebo	Esmethadone	LS Mean Difference (esmethadone - placebo)
Intent to Treat	N=41	N=46	
Value at Day 28, Mean (SD)	23.1 (11.0)	17.4 (9.6)	
LS Mean (SE)	-13.27 (1.74)	-17.33 (1.60)	-4.06 (2.3)
95% CI	(-16.73, -9.82)	(-20.51, -14.15)	(-8.76, 0.64)
p-value			0.0892
Effect size			-0.38
	Placebo	Esmethadone	LS Mean Difference (esmethadone – placebo)
Per Protocol	N=32	N=42	
Value at Day 28, Mean (SD)	23.8 (10.5)	17.4 (9.7)	
LS Mean (SE)	-11.80 (1.72)	-17.44 (1.57)	-5.64 (2.33)
95% CI	(-15.24, -8.37)	(-20.57, -14.32)	(-10.29, -1.00)
p-value			0.0180
Effect size			-0.56