Long-Term Safety and Efficacy of Esmethadone in Patients With Major Depressive Disorder:

Findings From a 12-Month Open-Label Study

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Abstract

Background: Esmethadone is a novel *N*-methyl-D-aspartate receptor (NMDAR) uncompetitive antagonist in development as adjunctive treatment for major depressive disorder (MDD).

Methods: This 12-month, open-label study evaluated the safety and efficacy of esmethadone in patients with MDD meeting *DSM-5* criteria who completed 1 of 3 double-blind studies (*rollover*) and in patients with MDD and no prior participation in esmethadone studies (*de novo*). Safety was assessed from adverse events, laboratory parameters, vital signs, electrocardiogram, and the Columbia-Suicide Severity Rating Scale. Efficacy assessments used measures of depression, anxiety, sleep, sexual function, cognitive function, and quality of life. The safety population comprised patients who received at least 1 dose of study drug, and the full analysis set (FAS) comprised patients who had at least 1 postbaseline efficacy assessment.

Results: Safety population included 624 patients; FAS included 586 patients (384 *rollover* and 202 de novo); mean age was 42.9 (13.6) years, and mean baseline Montgomery-Åsberg Depression Rating Scale (MADRS10) was 34.5 (4.8). Most common treatment-related treatment-emergent adverse events were headache (4.6%), nausea (4.2%), and dizziness (2.6%). There were no signals of meaningful neurological, cardiovascular, metabolic, or sexual adverse events and no case of suicide or suicidal attempt. For the FAS, mean (SD) change from baseline for MADRS10 at 3, 6, 9, and 12 months was −20.1 (10.7), −21.0 (10.8), −21.6 (10.7), and −21.6 (10.4). For the de novo population, mean (SD) was −19.9 (10.0), −19.9 (10.4), −20.1 (10.2), and −22.5 (9.7). Consistent improvements occurred with other tested efficacy measures.

Conclusions: Long-term treatment with esmethadone was safe and well tolerated. The antidepressant efficacy of esmethadone was sustained over 12 months.

Trial Registration: ClinicalTrials.gov identifier: NCT04855760.

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Major depressive disorder (MDD) is a leading cause of disability and disease burden in the United States.[1] Using data from the National Epidemiologic Survey on Alcohol and Related Conditions-III, the 12-month prevalence of MDD was 10.4%, and the lifetime prevalence was 20.6%.[2] Unfortunately, as many as 50%–60% of patients with MDD fail to achieve an adequate response following initial treatment with an antidepressant.[3] Currently, 5 oral drugs are approved by the US Food and Drug Administration (FDA) as adjunctive treatment for MDD in patients who fail to adequately respond to first-line antidepressants: cariprazine, aripiprazole, brexpiprazole, olanzapine, and quetiapine. These 5 drugs are all second-generation antipsychotics with class-specific metabolic, cardiovascular, and neurological side effects. Thus, an unmet need exists for novel effective, safe and well-tolerated adjunctive treatments for MDD.

In recent years, the neurobiology of MDD is moving away from the classic serotonergic hypothesis,[4] and concerns have been raised about the risk-benefit profile of monoaminergic antidepressants.[5] An alternative

Clinical Points

- The long-term safety and tolerability and long-term durability of antidepressant effects with esmethadone have not been reported.
- This study confirmed a favorable safety and tolerability with esmethadone, and no new signal of weight gain, metabolic, cardiovascular, neurological, or sexual side effects.
- A durable improvement in major depressive disorder symptoms for up to 1 year was observed with esmethadone with high rates of response and remission.

hypothesis for the neurobiology of MDD suggests impairment of neural plasticity as a mechanism.[6–8] The role of *N*-methyl-D-aspartate receptors (NMDARs) in neural plasticity is well established,[9,10] and dysregulation of glutamatergic signaling via NMDARs is increasingly recognized as a potential pathological mechanism for neuropsychiatric disorders and a target for developing novel antidepressants.[11–16] Uncompetitive NMDAR antagonist antidepressants include intranasal esketamine, FDA approved for treatment-resistant depression and for MDD with suicidal ideation and oral twice daily dextromethorphan-bupropion, FDA approved as monotherapy for MDD. Current literature suggests that NMDAR uncompetitive antagonists, including esmethadone (REL-1017), are at the forefront among novel antidepressant candidates.[11,12,16]

Esmethadone, the dextro-enantiomer of racemic methadone, is a low affinity, low-potency NMDAR uncompetitive antagonist that binds to the phencyclidine site of the NMDAR at low-micromolar half-maximal inhibitory concentrations.[17,18] Esmethadone has 20-40-fold lower affinity for mu opioid receptors compared with levomethadone[19,20] and does not contribute to the opioid agonist effects of racemic methadone, which are attributed to its levoenantiomer, levomethadone.[17,21–24] Within the racemic methadone compound, esmethadone may function as an opioid antagonist to reduce the opioid agonist effects of levomethadone.[24,25] Clinical studies have confirmed that esmethadone lacks meaningful abuse potential[26] and does not cause withdrawal upon abrupt discontinuation.[19,27,28] Esmethadone was effective in preclinical models of depressive-like behavior,[29,30] restored neural plasticity through a brain-derived neurotrophic factor (BDNF)–dependent mechanism,[29] and increased BDNF serum levels in healthy adults.[31] Esmethadone demonstrated a favorable tolerability and safety profile across multiple clinical studies[19,26–28,32] and showed favorable tolerability and efficacy as adjunctive treatment of MDD in phase 2 and in phase 3 trials.[19,28] In the phase 2 trial of 25 and 50 mg esmethadone as adjunctive treatment of MDD in hospitalized patients, the efficacy endpoint was met with both doses.[28] In the phase 3 study of esmethadone as adjunctive treatment in outpatients, the primary endpoint was not met, but the study reached statistical significance in the key secondary endpoint of response rate ($P = .044$); the prespecified supportive analysis in the per-protocol population of patients completing treatment without major protocol deviations showed a $P = .056$; post hoc, efficacy was seen in the severe depression subgroup of patients with Montgomery-Åsberg Depression Rating Scale (MADRS) baseline score ≥35 ($P = .01$).[19] The phase 3 study of esmethadone as a monotherapy antidepressant confirmed its tolerability and safety profile but did not meet the primary endpoint (results posted at ClinicalTrials.gov; NCT05081167). Overall, the safety and efficacy results seen in esmethadone studies encourage its development as adjunctive treatment of MDD (Supplementary Table 3).[19,26–28,32] Two phase 3 studies of esmethadone as adjunctive treatment of MDD are underway (NCT04855747 and NCT06011577).

The objective of this open-label study was to evaluate the long-term safety and tolerability, as well as the long-term durability of the antidepressant effects of esmethadone.

METHODS

This multicenter trial was conducted in accordance with the International Council on Harmonisation 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 patients after receiving a complete description of the study and prior to any study procedures. The study was registered at clinicaltrials.gov: NCT04855760.

Study Design

This was a multicenter, open-label, 12-month study of esmethadone to evaluate the long-term safety and long-term durability of response in patients with MDD. Patients with MDD who previously completed randomized, double-blind phase 3 trials of esmethadone as adjunctive therapy (NCT04688164 and NCT04855747) or as monotherapy (NCT05081167) were asked to continue treatment with esmethadone 25 mg daily (*rollover* patients). This trial also enrolled de novo patients, without prior participation in esmethadone trials; these patients received a 75 mg loading dose of esmethadone on day 1 followed by a maintenance dose of esmethadone 25 mg daily for the remainder of the study (days 2–365). When esmethadone was administered as adjunctive treatment, rollover and de novo patients continued to use their stable dose of concomitant antidepressants.

Patient Selection

Rollover patients from previous esmethadone studies were not rescreened prior to enrollment, and their eligibility was based on inclusion/exclusion criteria for each trial (NCT04688164, NCT04855747, and NCT05081167). De novo patients were men or women age 18–65 years diagnosed with MDD based on the Structured Clinical Interview for *DSM-5* Disorders consistent with the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition, experiencing a current major depressive episode lasting from 8 weeks to 36 months. Patients had a Hamilton Depression Rating Scale-17[33] score ≥19 at Screening and independently verified by a Massachusetts General Hospital-Clinical Trials Network and Institute (MGH-CTNI)-certified clinician interviewing the patient off-site using the SAFER interview[34] and the Antidepressant Treatment Response Questionnaire (ATRQ).[35] De novo patients also were required to have a Montgomery-Åsberg Depression Rating Scale [10-item questionnaire] (MADRS10)[36] score ≥24 at baseline. When esmethadone was administered as adjunctive treatment, patients had an inadequate response (<50% improvement) to 1–3 approved antidepressant medications administered adequately for at least 6 weeks confirmed by MGH-ATRQ. Approved antidepressants included selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, bupropion (a norepinephrine-dopamine reuptake inhibitor), and nicotinic receptor antagonists (see Supplementary Table 1). In the event of discontinuation of any approved antidepressant, the discontinuation occurred at least 6 weeks prior to baseline. An electronic dosing diary (eDiary) was used to document the stability of background antidepressants; only patients reporting a minimum of 80% adherence during screening were randomized. Patients were excluded for any medical or psychiatric condition, or social context that could unfavorably alter the risk benefit of participation, interfere with protocol compliance, or confound safety or efficacy assessments (see Supplementary Material for complete inclusion and exclusion criteria).

Study Assessments

Safety was assessed with physical examinations, vital signs (heart rate, blood pressure, respiratory rate, body temperature, and pulse oximetry), and clinical laboratory testing (chemistry, hematology, and urinalysis) at baseline and at 1 month (de novo patients only) and 3, 6, 9, and 12 months (all patients). For de novo patients, an electrocardiogram (ECG) was obtained predose at baseline and day 7 and 2.5 hours (±10 minutes) postdose at month 1 (de novo patients only); for all patients, an ECG was obtained 2.5 hours (±10 minutes) postdose at 3, 6, and 12 months. The QT interval with Fridericia correction (QTcF) was calculated for all ECGs. Safety assessments included Columbia-Suicide Severity Rating Scale (C-SSRS)[37] and Clinician-Administered Dissociative States Scale (CADSS)[38] assessed at baseline and at 3, 6, 9, and 12 months and the Misuse, Abuse, and Diversion Drug Event Reporting System (MADDERS)[39] at each treatment visit.

MADRS10, Clinical Global Impression of Improvement (CGI-I) and Severity (CGI-S),[40] and Hamilton Anxiety Rating Scale (HAM-A)[41] were obtained at baseline and at 3, 6, 9, and 12 months. Symptoms of Depression Questionnaire (SDQ),[42] Sheehan Disability Scales (SDS),[43] Patient-Reported Outcomes Measurement Information SystemSleep Disturbance (PROMIS-SD),[44] Digit Symbol Substitution Test (DSST),[45] Perceived Deficits Questionnaire-Depression (PDQ-D-5)—cognition scale,[46] Treatment Satisfaction Questionnaire for Medication (TSQM),[47] SF-12 Physical and Mental Health Summary Scale (SF-12),[48] EuroQol 5-level EQ-5D questionnaire version (EQ-5D-5L),[49] Work Productivity and Activity Impairment Instrument (WPAI: SHP),[50] and Arizona Sexual Experience Scale (ASEX)[51] were obtained at baseline and at month 6 and month 12. Details of study assessments are provided in Supplementary Table 2.

Statistical Analysis

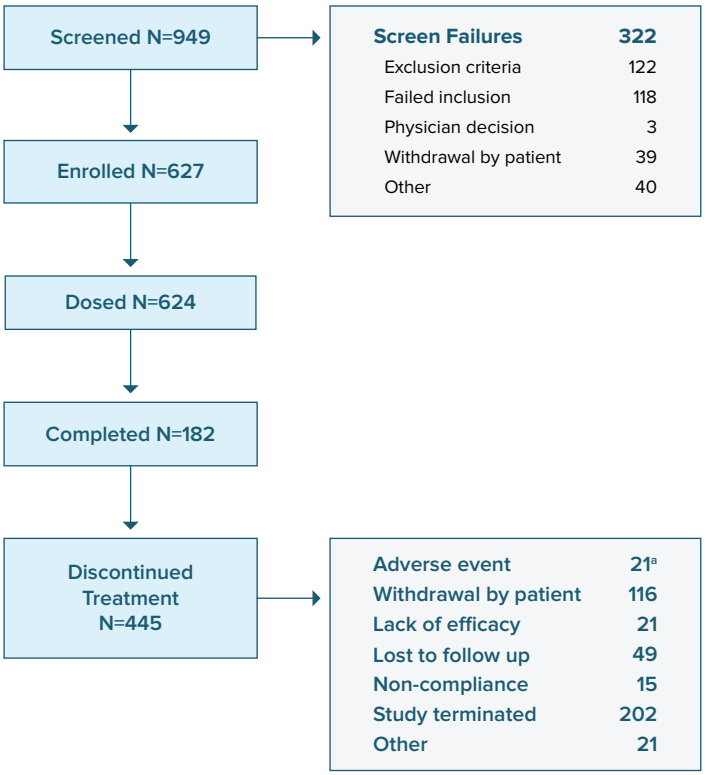
To evaluate overall safety of esmethadone, the sample size for the open-label study aimed to achieve at least 300 patients completing 6 months and at least 100 patients completing 12 months of the study. The study planned to enroll up to approximately 1,200 patients to allow for an estimated drop-out rate of 35%. The safety set included all patients who received at least 1 dose of study drug. The full analysis set (FAS) comprised all patients who received at least 1 dose of study drug and had at least 1 postbaseline efficacy assessment, irrespective of any deviation from the protocol or premature discontinuation.

Descriptive statistics were applied for all safety and efficacy assessments. Total FAS data set includes de novo patients and rollover patients from randomized studies (NCT04688164, NCT04855747, and NCT05081167). Rollover baseline score is the last nonmissing value prior to the first double-blind dose; de novo baseline score is the last nonmissing value prior to the first open-label dose. Month 12 are patients that completed month 12 visit; month 13 are follow-up visits that occurred after month-12 visit. Efficacy results are presented for the FAS set, and safety results for the safety set. End of treatment (EOT) is the last day of treatment with esmethadone.

RESULTS

A total of 949 patients were screened for the study, and 627 were enrolled. The Safety Population included

Figure 1.
Disposition



[a]While 37 patients were recorded as having an TEAE that led to discontinued study medication (Table 2), only 21 were recorded as having adverse event as their "reason for terminating study drug."
Abbreviation: TEAE = treatment-emergent adverse event.

420 (67.3%) patients who were rollover from double-blind studies and 204 (32.7%) de novo patients and comprised 624 patients; the FAS population comprised 586 patients (Figure 1). At baseline, mean age was 42.9 years, 69.4% were female, and 76.0% were Caucasian (Table 1). For the safety population, mean (SD) time since the first MDD diagnosis was 15.6 (11.4) years.

Safety/Tolerability

At least 1 treatment-emergent adverse event (TEAE) was reported by 350 (56.1%) patients. At least 1 treatment-related TEAE was reported by 170 (27.4%) patients (Table 2). The most common TEAEs were COVID-19 infection (9.6%), headache (9.8%), upper respiratory tract infection (8.5%), and nausea (5.1%). The most common treatment-related TEAEs were headache (4.6%), nausea (4.2%), and dizziness (2.6%). Eight (1.3%) patients experienced 11 serious adverse events (AEs) (coronary artery disease 1 [0.2%]; tachycardia 1 [0.2%]; alcohol abuse 1 [0.2%]; anxiety 1 [0.2%]; anaphylactic reaction 1 [0.2%]; bacteremia 1 [0.2%]; pyelonephritis 1 [0.2%]; sepsis 1 [0.2%]; hyperglycemia 1 [0.2%]; hyperreflexia 1 [0.2%]; tremor 1 [0.2%]); none of the serious AEs were considered treatment-related. TEAEs leading to discontinuation of esmethadone occurred in 37 (5.9%) patients, and 22 (3.5%) patients discontinued for treatment-related TEAEs.

At baseline, 85/624 (13.6%) patients had suicidal ideation, and 2 (0.3%) had nonsuicidal self-injurious behavior on the C-SSRS, while at 12 months, 16/201 (8.0%) patients had suicidal ideation and 1/201 (0.5%) had nonsuicidal self-injurious behavior. Mean (SD) CADSS scores were 0.6 (2.1) at baseline and 0.2 (1.0) at month 3, a change from baseline of −0.3 (2.0) for 536 patients who had baseline and month 3 CADSS values; the mean CADSS scores were 0.2 (0.9) at month 12/EOT, a change from baseline of −0.6 (2.9) for 196 patients who had baseline and EOT CADSS values.

Vital signs remained stable throughout the 12-month trial. Mean (SD) body weight was 79.2 (16.4) kg at baseline and 79.0 (16.8) kg at month 12. Mean body mass index was 27.8 (4.3) kg/m^2 at baseline and 27.7 (4.5) kg/m^2 at month 12. Mean (SD) supine/semisupine diastolic and systolic blood pressure were 76.3 (8.0) and 121.4 (11.9) mm Hg at baseline, respectively, and

Table 1.

Baseline Characteristics (Safety Population)

Characteristics	Patients (n = 624)
Age, y[a]	42.9 ± 13.6
Body mass index. kg/m²[a]	27.8 ± 4.3
Body weight, kg[a]	79.0 ± 16.3
Female, n (%)	433 (69.4)
Ethnicity	
Hispanic or Latino	162 (26.0)
Not Hispanic or Latino	442 (70.8)
Not reported	17 (2.7)
Unknown	3 (0.5)
Race	
American Indian or Alaska Native	1 (0.2)
Asian	24 (3.8)
Black or African American	95 (15.2)
Native Hawaiian or Other Pacific Islander	1 (0.2)
Caucasian	474 (76.0)
Multiracial	16 (2.6)
Other	13 (2.1)
Time since first diagnosis of MDD, y[a]	15.6 ± 11.4
Age MDD began impacting function, y[a]	26.0 ± 13.7
Number of lifetime depressive episodes[a]	6.7 ± 9.0
Number of depressive episodes in past 5 y[a]	2.3 ± 1.7
Duration of current major depressive episode, y[a]	1.0 ± 1.4

[a]Mean ± standard deviation.
Abbreviation: MDD = major depressive disorder.

Table 2.

Treatment-Emergent Adverse[a] Events and Treatment-Related Adverse Events[b]

Safety population (N = 624)	Number (%)
At least 1 TEAE	350 (56.1)
At least 1 treatment-related TEAE	171 (27.4)
At least 1 serious TEAE	8 (1.3)
At least 1 serious treatment-related TEAE	0
TEAE leading to study discontinuation	37 (5.9)
Treatment-related TEAEs leading to discontinuation	22 (3.5)
Treatment-emergent adverse events occurring in 5% or more patients	
COVID-19	60 (9.6)
Headache	61 (9.8)
Upper respiratory tract infection	53 (8.5)
Nausea	32 (5.1)
Most common treatment-related TEAE	
Headache	29 (4.6)
Nausea	26 (4.2)
Dizziness	16 (2.6)

[a]TEAE: adverse event that started or worsened after starting treatment.
[b]Treatment-related TEAE: TEAE categorized as possibly, probably, or definitely related.
Abbreviation: TEAE = treatment-emergent adverse event.

75.6 (7.9) and 122.2 (12.3) mm Hg at month 12. At baseline, mean (SD) supine/semisupine heart rate was 70.0 (10.4) beats/min and 69.9 (10.4) beats/min at month 12.

Mean (SD) QTcF interval was 406.5 (18.6) ms at baseline and 408.8 (20.9) at month 12, a change from baseline (CFB) of 2.6 (13.8). At baseline, 5 (0.8%) of 624 patients had a QTcF interval >450 ms. The worst postbaseline QTcF interval was >450–480 ms in 33 (5.3%) patients and >480–500 ms in 4 (0.6%) patients; no patient had a QTcF over 500 ms. A worst postbaseline increase of ≥30 to <60 ms was seen in 58 (9.3%) patients and >/=60 msec in 1 (0.2%) patient; no patient met the criteria for an AE due to QTcF prolongation (worst postbaseline value >500 ms and an increase >60 ms). A 65-year-old male patient had a grade 2 elevation in the QT, which was considered unlikely related to therapy; however, the patient was discontinued from the study.

The potential for misuse, abuse, and diversion of esmethadone was evaluated with MADDERS. Among the safety population of 624 patients, 57 MADDERS cases were identified and adjudicated in 49 patients. Among the 57 cases, none were adjudicated as "abuse," 2 were adjudicated as "misuse," 6 as "therapeutic error," 34 as "none of these," and 15 as "unable to classify."

Efficacy

For the FAS population, mean baseline MADRS10 score was 34.5 (4.8), and mean CGI-S score was 4.8 (0.7). Mean MADRS10 total score decreased from baseline to month 3 by 20.1 points, and the CFB was sustained through month 12 (Table 3; Figure 2). Mean (SD) CFB for the MADRS was −20.1 (10.7), −21.0 (10.8), −21.6 (10.7), and −21.6 (10.4) at 3, 6, 9, and 12 months, respectively. In the de novo population, mean CFB for the MADRS was −19.9 (10.0), −19.9 (10.4), −20.1 (10.2), and −22.5 (9.7) at 3, 6, 9, and 12 months, respectively. In the FAS group, response rates at 3 and 12 months were 63.9% and 69.2%, and remission rates at month 3 and month 12 were 44.7% and 48.8%, respectively. In the de novo group, response rates at 3 and 12 months were 60.7% and 77.2%, and remission rates at month 3 and month 12 were 44.0% and 54.4%, respectively (Supplementary Figure 1).

Mean (SD) CGI-S score decreased from 4.8 (0.7) at baseline to 2.5 (1.2) at month 12, and in the de novo group, from 4.8 (0.6) to 2.4 (1.2) (Figure 2). CGI-I scores at 12 months were improved (score of ≤3) in 89.4% of the FAS group and 96.5% of de novo patients. At least 67.2% of patients were much or very much improved by month 3 on the CGI-I scale and increased through month 12–73.9% (Figure 2). Mean (SD) HAM-A score decreased from baseline of 20.4 (5.8) to 9.2 (7.1) at month 12 in the FAS group and from 20.6 (5.9) to 8.4 (5.7) in the de novo group (Figure 2).

CFB on additional efficacy measures, including PROMIS-SD, DSST, PDQ-D5, TSQM, SF-12v2 mental health, SF-12v2 physical health, EQ-5D-5L, WPAI-SHP, ASEX, SDQ, and SDS, are reported in Table 3. At baseline, mean (SD) scores were similar between FAS and de novo populations; at month 12, improvement in

Table 3.

Change From Baseline for Study End Points (FAS Population)

	Mean ± SD			
	FAS (N = 586)		De novo (N = 202)	
Variable	Baseline[a]	Change from baseline at month 12	Baseline[a]	Change from baseline at month 12
MADRS10	34.5 ± 4.8	−21.6 ± 10.4	33.8 ± 4.5	−22.5 ± 9.7
CGI-S	4.8 ± 0.7	−2.2 ± 1.3	4.8 ± 0.6	−2.4 ± 1.2
HAM-A	20.4 ± 5.8	−11.9 ± 7.4	20.6 ± 5.9	−13.5 ± 7.1
PROMIS-SD	31.3 ± 6.3	−9.8 ± 9.6	31.7 ± 6.2	−9.2 ± 8.3
DSST	47.8 ± 16.3	8.4 ± 13.8	47.3 ± 14.8	5.8 ± 11.9
PDQ-D5	12.1 ± 4.1	−4.8 ± 4.4	11.9 ± 4.4	−4.7 ± 3.9
TSQM	40.7 ± 11.3	8.5 ± 15.7	44.2 ± 13.0	7.2 ± 17.0
SF-12v2 mental health	17.2 ± 2.7	4.0 ± 3.8	17.5 ± 2.9	3.8 ± 2.9
SF-12v2 physical health	17.8 ± 2.8	0.3 ± 2.7	17.6 ± 2.9	0.3 ± 2.6
EQ-5D-5L	9.8 ± 2.4	−2.5 ± 2.7	9.8 ± 2.4	−2.9 ± 2.4
WPAI-SHP	36.0 ± 25.2	−3.4 ± 22.0	36.3 ± 26.1	−3.5 ± 21.8
ASEX	20.9 ± 5.4	−2.9 ± 5.5	20.4 ± 5.4	−3.2 ± 5.0
SDQ	156.7 ± 23.8	−45.9 ± 29.4	158.3 ± 26.8	−43.7 ± 30.9
SDS	12.6 ± 3.9	−8.2 ± 5.2	12.2 ± 4.1	−7.6 ± 4.7

[a]For rollover patients (REL-1017-301, REL-1017-302, and REL-1017-303), the baseline score was the last nonmissing value prior to the first double-blind dose; for de novo patients, the baseline score was the last nonmissing value prior to the first open-label dose.

Abbreviations: ASEX = Arizona Sexual Experience Scale; CGI-S = Clinical Global Impression-Severity; DSST = Digit Symbol Substitution Test; EQ-5D-5L = EuroQol 5-level EQ-5D questionnaire version; HAM-A = Hamilton Anxiety Rating Scale; MADRS = Montgomery-Åsberg Depression Rating Scale; PDQ-D5 = Perceived Deficits Questionnaire-Depression—cognition scale; PROMIS-SD = Patient-Reported Outcomes Measurement Information System-Sleep Disturbance; SDQ = Symptoms of Depression Questionnaire; SDS = Sheehan Disability Scale; SF-12 = SF-12 Physical and Mental Health Summary Scale; TSQM = Treatment Satisfaction Questionnaire for Medication; WPAI:SHP = Work Productivity and Activity Impairment Instrument.

scores for all assessments was observed in both FAS and de novo populations (Table 3).

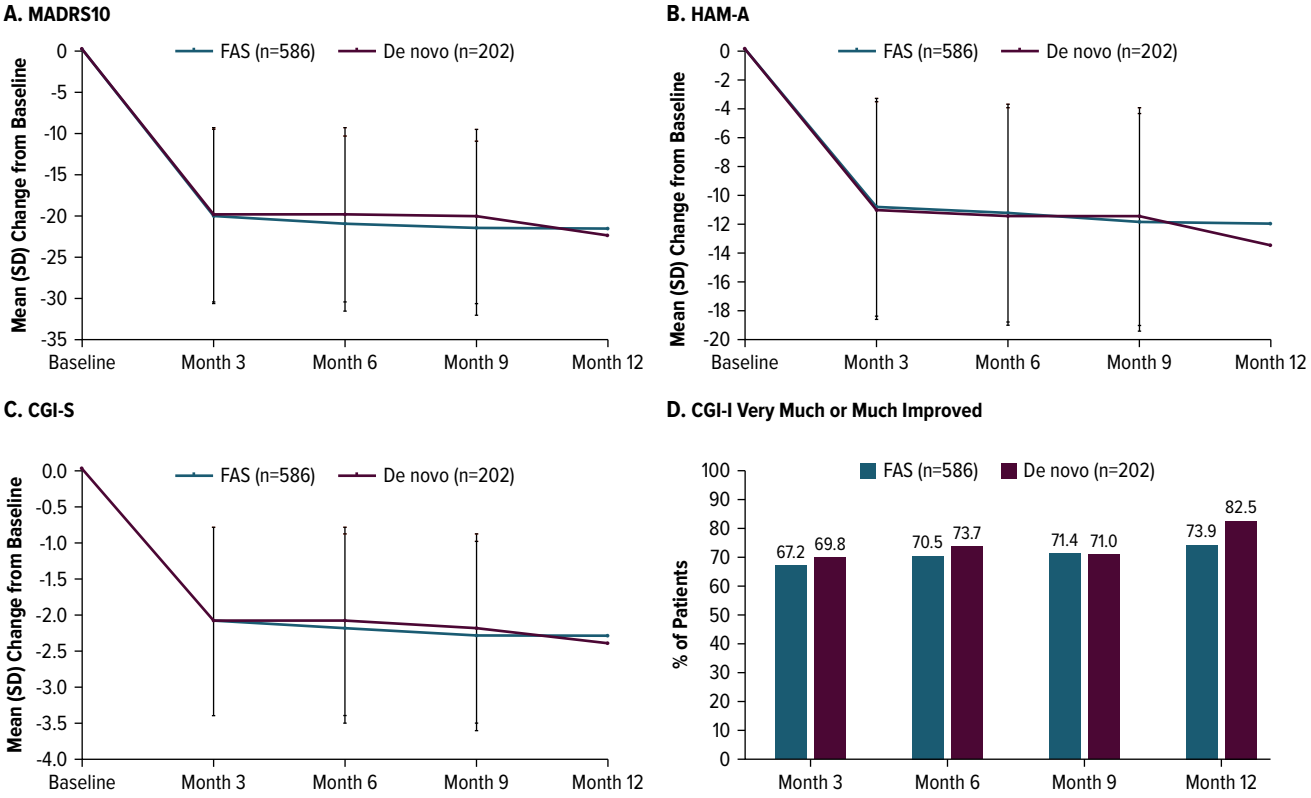
DISCUSSION

In this open-label trial that followed patients with MDD for 1 year, esmethadone was safe and well tolerated, consistent with results observed in other esmethadone trials.[19,26–28,32] Study drug discontinuation due to TEAEs occurred in 37 (5.9%) patients; for 22 (3.5%) of these patients, TEAEs leading to discontinuation of study drug were categorized as treatment-related. The most commonly reported treatment-related TEAEs occurred at rates less than 5% and included headache (4.6%), nausea (4.2%), and dizziness (2.6%). Importantly, no meaningful safety signal was observed for weight gain, sexual dysfunction, cardiovascular safety, and neurological or dissociative effects. There were no cases of suicide or suicidal attempts and no treatment-related SAEs. No meaningful signal for abuse potential was observed throughout this 12-month open-label trial, and no cases of withdrawal syndrome occurred after discontinuation, confirming the lack of meaningful opioid agonist activity seen in previous preclinical[22,24] and clinical studies.[26] No cases were classified as "abuse" or "withdrawal" on the MADDERS. Two of the 57 MADDERS cases were classified as "misuse": both patients reported doubling the dose on a few occasions, with the intent of relieving depression. Both patients were redirected to take the medication as prescribed (1 tablet per day) and were continued in the trial without further compliance issues. These MADDERS results suggest no meaningful risk for abuse potential with esmethadone and are consistent with prior clinical studies evaluating the abuse potential of esmethadone.[26] QTcF prolongation compared to baseline was overall modest and consistent with prior clinical results. There were no AEs related to QTcF prolongation.

Among this population of patients with moderate-to-severe MDD, as evidenced by a baseline MADRS10 score of 34, we observed meaningful and durable antidepressant effects (CFB for MADRS10 score of >20 points) and meaningful response rate (approximately 70% at month 12) and remission rate (approximately 50% at month 12). Clinically meaningful improvements on efficacy measures were noted at month 3 (first efficacy assessment for the FAS population) and were sustained through month 12 (Figure 2; Table 3). Consistently, improvements were also observed for measures of quality of life, sexual function, and cognitive function (Table 3). Esmethadone did not elicit psychoactive AEs, including no euphoria and no dissociative effects. Esmethadone improved scores for

Figure 2.

Mean Change From Baseline for (A) MADRS10, (B) HAM-A, and (C) CGI-S Over Time and (D) Proportion of Patients Very Much or Much Improved on the CGI-I



Abbreviations: CGI-I = Clinical Global Impression of Improvement, CGI-S = Clinical Global Impression-Severity; FAS= full analysis set, HAM-A = Hamilton Anxiety Rating Scale; MADRS = Montgomery-Åsberg Depression Rating Scale.

both the DSST and the PDQ-D5, which are measures of cognitive function (Table 3).

Limitations of this study included its open-label design with no comparator group. Potential biases were inclusion of patients selecting for enrollment in the open-label extension vs those not enrolling, vs enrollment of de novo patients. The design of the study may have enriched for rollover patients who responded to esmethadone, while patients experiencing AEs or nonresponders during the 28-day randomized studies may have opted not to participate. In addition, analyses of the individual courses of patients were not done. Specific studies to understand drug-drug interactions and esmethadone exposure in patients with renal and hepatic impairment have been performed.[32] However, further evaluation of the safety of esmethadone may be necessary to better understand the risks in patients with underlying conditions and polypharmacy. Overall, in this open-label study, esmethadone was safe and well tolerated, and patients experienced sustained CFB improvement in all tested efficacy scales, both in the FAS and de novo populations.

In summary, the results from this study are consistent with previous clinical studies of esmethadone[19,26–28,32] and confirm favorable safety and tolerability with a low incidence of treatment-related AEs and no signal for metabolic, cardiovascular, neurological, or sexual side effects (Supplementary Table 3). There was no signal for abuse or withdrawal, and there were no AEs related to QTcF prolongation. Esmethadone produced a robust and durable improvement in MDD symptoms for up to 1 year with high rates of response and remission, together with improvement in assessments of functional and cognitive symptoms. Esmethadone is a promising safe and well-tolerated novel adjunctive antidepressant candidate with the potential to meaningfully improve outcomes in patients with MDD unresponsive to first-line antidepressants.

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Supplementary Material

Article Title: Long-Term Safety and Efficacy of Esmethadone in Patients with Major Depressive Disorder: Findings from a 12-Month Open-Label Study

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LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

DISCLAIMER

Supplementary Appendix

Supplementary Table 1. Allowed background antidepressant therapy

SSRI	Minimally adequate dose
paroxetine	20 mg QD
fluoxetine	20 mg QD
sertraline	50 mg QD
citalopram	20 mg QD (Maximum allowed dose 40 mg QD)
escitalopram	10 mg QD (Maximum allowed dose 20 mg QD)
vilazodone	40 mg QD
vortioxetine	10 mg QD

SNRI	Minimally adequate dose
venlafaxine/venlafaxine XR	150 mg QD
desvenlafaxine	50 mg QD
duloxetine	60 mg QD or 30 mg BID
levomilnacipran	40 mg QD

Tricyclics and Tetracyclics	Minimally adequate dose
amitriptyline	150 mg QD
amoxapine	150 mg QD
clomipramine	150 mg QD
doxepin	150 mg QD
desipramine	150 mg QD
imipramine	150 mg QD
maprotiline	150 mg QD
nortriptyline	75 mg QD
protriptyline	30 mg QD

Other Antidepressant Therapy	Minimally adequate dose
bupropion	300 mg QD
mirtazapine	15 mg QD
trazodone	300 mg QD

Detailed Inclusion and Exclusion Criteria

Inclusion Criteria

All participants who complete esmethadone Phase 3 studies without any safety issues that would preclude participation in this open-label extension (according to the Investigator) are eligible.

Esmethadone-310 *de novo* participants will undergo Screening assessments and must meet all the following inclusion criteria to participate in this study.

1. Must be able to read, speak, and understand English or Spanish and must provide written informed consent prior to the initiation of any protocol-specific procedures.
2. Male or female participant, age 18 to 65 years, inclusive.
3. BMI between 30.1 and 35.0 kg/m2 at Screening.
4. Participant is willing and able to commit to meet all study requirements, adhere to both approved ADT (as applicable) and study drug regimen, and complete all assessments and all scheduled visits, per Investigator judgment.
5. WOCBP and men whose sexual partners are WOCBP must use at least 1 highly effective method of contraception from Screening and for at least 2 months after the last study drug administration. For men with female sexual partners of childbearing potential, examples of medically acceptable forms of contraception include vasectomy or male condom for participants, plus an additional method of contraception for their female partners. Highly effective methods of contraception are those which have a failure rate of <1% (when implemented consistently and correctly) and include:
   - IUD
   - Bilateral tubal ligation, bilateral salpingectomy, or bilateral tubal occlusive procedure o Hormonal contraceptives (e.g., oral, patch, or injectable)
   - A double-barrier protection method (e.g., condom, sponge, or vaginal diaphragm with
   - spermicide cream, foam, or gel)
   - Abstinence from heterosexual intercourse is accepted if this is the participant's usual lifestyle and must be continued until at least 2 months after the last dose of study drug.

Women who are not of childbearing potential must be congenitally or surgically sterile (hysterectomy and/or bilateral oophorectomy/salpingo-oophorectomy, as determined by the participant's medical history) or must be post-menopausal. Post-menopausal is defined as being amenorrheic for at least 1 year without another cause and FSH level ≥40 mIU/mL as confirmation.

6. Diagnosed with MDD as defined by the DSM-5, and confirmed by the SCID-5.
7. Hamilton Depression Rating Scale-17 (HAMD17) score ≥19 at Screening and independently confirmed by **S**tate versus trait; **A**ssessability; **F**ace validity; **E**cological validity; and **R**ule of three Ps [pervasive, persistent, and pathological] (SAFER) assessment.
8. At Baseline, before definitive admission and randomization of the participant, the MADRS10 scale will be administered and the participant must show a MADRS10 score ≥24.
9. Diagnosed with a current major depressive episode (MDE) lasting from 8 weeks to 36 months as defined by the DSM-5 and confirmed by the SCID-5 for MDD, as well as independent confirmation of the HAMD17 score, SAFER/Antidepressant Treatment

Response Questionnaire (ATRQ), and contextual appropriateness to be a participant in this study, after evaluation by a Massachusetts General Hospital (MGH)-Clinical Trials Network and Institute (CTNI) certified clinician.

For *de novo* participants enrolling for esmethadone adjunctive therapy:

10. Treated for at least 6 weeks prior to Screening and stabilized for at least 6 weeks prior to Baseline on an approved dosing regimen of ADT medications (e.g., selective serotonin reuptake inhibitor [SSRI], serotonin and norepinephrine reuptake inhibitor [SNRI], bupropion (a norepinephrine–dopamine reuptake inhibitor [NDRI] and nicotinic receptor antagonist) during the current MDE, and committed to remaining on the same stable dosing regimen during the Screening period and for the entire study duration, at or above the minimally adequate dose in the ATRQ. Maximal doses and recommended doses for each ADT are at the discretion of the Investigator and Medical Monitor, except for citalopram and escitalopram (see Section 16).

Note: Discontinuation of any of the listed ADT must occur at least 6 weeks prior to Baseline.
Note: Participants taking trazodone and/or bupropion as secondary ADT are permitted.
Note: An electronic dosing diary (eDiary) will be used beginning at Screening to document the stability of background antidepressant(s); only participants reporting a minimum of 80% adherence during Screening will be randomized.

11. An appropriate and valid participant in the study, after independent MGH-CTNI SAFER/ATRQ assessment of the participant's MDD condition to confirm the diagnosis of MDD, as well as the inadequate response to 1 to 3 valid courses of treatment with an antidepressant medication in the current MDE, defined as <50% improvement with an antidepressant medication at doses listed on the SAFER and ATRQ Interview Forms.

For *de novo* participants enrolling for esmethadone monotherapy:

12. An appropriate and valid participant in the study, after independent MGH-CTNI SAFER/ATRQ assessment of the participant's MDD condition to confirm the diagnosis of MDD (Criteria: **S**tate versus trait; **A**ssessability; **F**ace validity; **E**cological validity; and **R**ule of three Ps [pervasive, persistent, and pathological]).

Exclusion Criteria

Esmethadone-310 *de novo* participants will undergo Screening assessments. Individuals meeting any of the following criteria are ineligible to participate in this study.

1. History or presence of clinically significant abnormality as assessed by physical examination, medical history, 12-lead ECG, vital signs, or laboratory values, which in the opinion of the Investigator, Medical Monitor, or Sponsor designee would jeopardize the safety of the participant or the validity of the study results, including established QT prolongation, long QT syndrome, torsades de pointes, bradyarrhythmia, ventricular tachycardia, uncompensated heart failure (greater than NYHA Class 1 CHF), uncontrolled hypokalemia, or uncontrolled hypomagnesemia.
2. More than class 2 angina pectoris or MI or acute coronary syndrome within the past 3 months.
3. Any medical, psychiatric condition, or social context that, in the opinion of the Investigator, Medical Monitor, or Sponsor designee is likely to unfavorably alter the risk-benefit of subject

participation, to interfere with protocol compliance, or to confound safety or efficacy assessments.

4. Have any significant illness, of any nature, including possible SARS-CoV-2 related fever and other symptoms, requiring hospitalization, emergency treatment, or isolation (quarantine) within 4 weeks prior to Screening or during the Screening period, and as determined by the Investigator.
5. History or first degree relative with history of unexplained sudden death or long QT syndrome.
6. Triplicate 12-lead ECG with average QTcF ≥450 msec, and/or a QRS interval ≥120 msec at Screening.
7. Current or recent uncontrolled orthostasis or orthostatic hypotension necessitating treatment.
8. Poorly controlled diabetes as defined by HbA1c >7.5%, despite standard care.
9. Any use of long-term prescribed opioids (i.e., >120 days in a 6-month period) within 6 months prior to Screening or any recreational use of opioids.
10. More than 3 doses of opioids within 30 days prior to Baseline.
11. Any use of benzodiazepine within 30 days prior to Baseline and/or more than 3 doses of antipsychotics, when used for non-psychiatric indications, within 30 days prior to Baseline.
12. Use of any anxiolytic, antipsychotic, anticonvulsant/antiepileptic, mood stabilizer, or stimulant medication(s) within 30 days prior to Baseline. Note: Participant should be medically stable, the medication was appropriately tapered and participant has no withdrawal symptoms.
13. Use of St. John's Wort within 30 days prior to Baseline.
14. Received ketamine, memantine, and/or dextromethorphan treatment within 30 days prior to Screening.
15. History of allergy or hypersensitivity to methadone or related drugs.
16. Any current and primary psychiatric disorder (i.e., a condition that is the primary focus of distress and/or treatment other than MDD), as defined by the DSM-5 and confirmed by psychiatric history and/or examination by the Investigator. These disorders include, but are not limited to, any psychotic disorder, post-traumatic stress disorder, borderline personality disorder, antisocial personality disorder, obsessive-compulsive disorder, intellectual disability, or pervasive developmental disorder.
17. Participants who, in the Investigator's judgment, are at significant risk for suicide. A participant with a C-SSRS ideation score of 4 or 5 within the last 6 months or any suicide attempt within the past year of either Screening or Baseline must be excluded.
18. Any lifetime history of bipolar I or II disorder, psychosis and/or mania as defined by the DSM-5 and confirmed by psychiatric history and/or examination by the Investigator.
19. Comorbid moderate to heavy alcohol or substance use disorder, as defined by DSM-5, at Screening or within the 12 months prior to Screening. Heavy drinking is defined as an average of 3 or more drinks per day, in the last month.
20. A positive result on the urine drug/alcohol screen within 30 days prior to Baseline (Day 1). At Investigator discretion, in consultation with the Medical Monitor or designee, a retest is permitted.
21. Increase in absolute value of >40% or a decrease in absolute value of >20% on the HAMD17 score between Screening and Baseline as conducted by the certified site rater.
22. Evidence of clinically significant hepatic or renal impairment, including an eGFR <60 mL/min/1.73 m2 (CKD-EPI 2009 calculation), ALT or AST >2.0 × ULN, bilirubin >1.5 × ULN (participants with history of Gilbert's syndrome diagnosis may be

included if approved by the Medical Monitor), or endocrine laboratory values (including clinically significant thyroid parameters, i.e., TSH < 0.9 x LLN or > 1.25 x ULN).
23. Diagnosed with and/or treated for any type of cancer (excluding basal cell carcinoma and in situ melanoma) within 4 years prior to Screening.
24. Any planned elective surgery requiring general anesthesia.
25. Participant has had gastric bypass surgery, or has had any procedures or disorders that are likely to significantly interfere with gastrointestinal transit or absorption.
26. Participated in a clinical study with an investigational medication in the past 6 months, or participated in more than 2 clinical studies with investigational medications in the past 2 years.
27. Females who are currently lactating.

For *de novo* participants enrolling for esmethadone monotherapy:
28. Use of any antidepressant medication within 30 days prior to Screening.

Supplementary Table 2. Schedule of study assessments for *rollover* and *de novo* participants

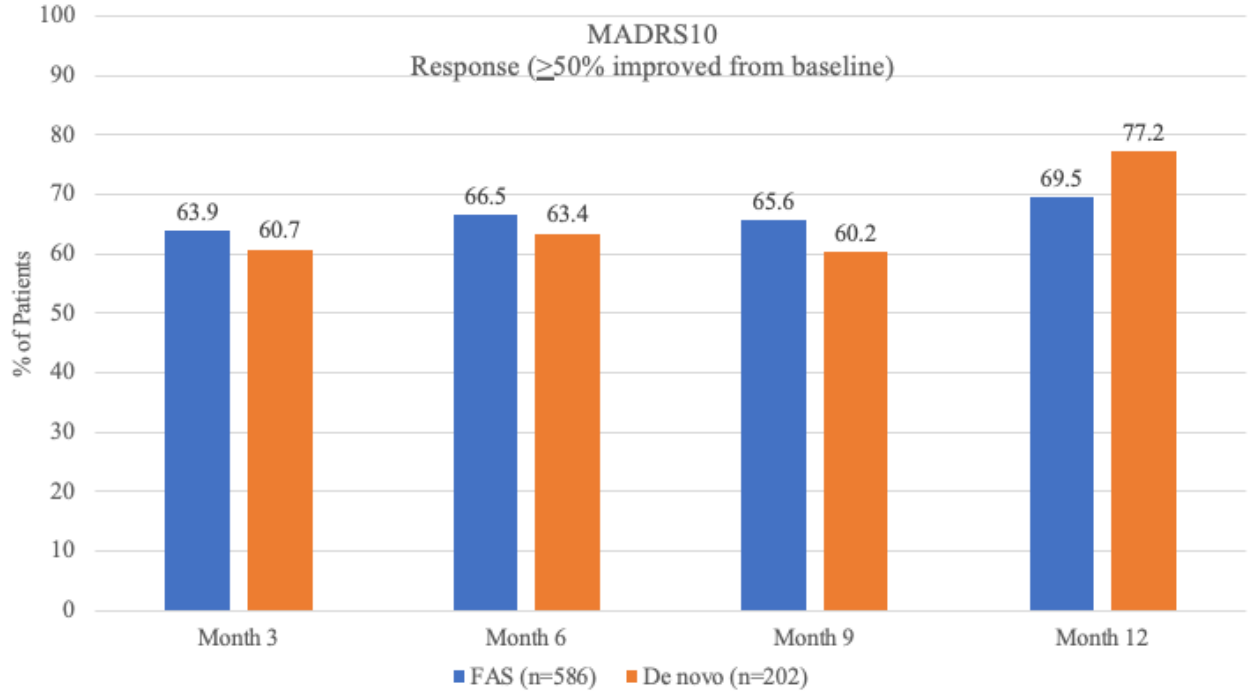
Rollover Participants

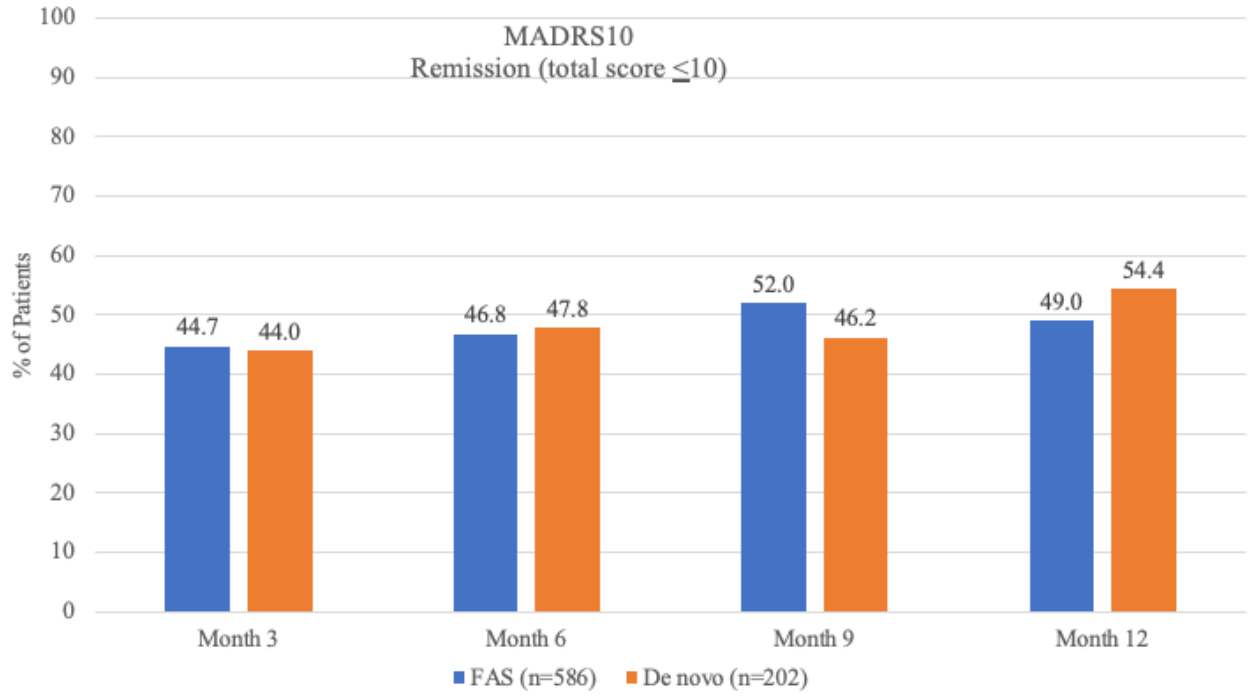
Main Study Visit*	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
	OLS Baseline Day 1†						**EOT/ET Day 365**	**EOS[a] Follow-up**
Telephone Contact**		**At 2-week (±2 days) intervals from previous month's visit**						
Assessment Month***	**0**	**D7 (±2d)**	**1 (±5d)**	**3 (±5d)**	**6 (±5d)**	**9 (±5d)**	**12 (±5d)**	**13 (±5d)**
Informed Consent	X							
Medical & Psychiatric History (changes)	X							
Demographics and Height (changes)	X							
Physical Examination[b]	X[b]				X[b]		X[b]	X[b]
Weight and BMI	X			X	X	X	X	X
Concomitant Medications/Therapies	X			X	X	X	X	X
Vital Signs (including body temperature) and Pulse Oximetry[c]	X			X	X	X	X	X
ECG[d]	X	X[d]		X	X		X	X
LABORATORY TESTING								
Hematology	X			X	X	X	X	X
Biochemistry[e]	X[d]			X	X	X	X[d]	X
Urinalysis	X			X	X	X	X	X
Drug Screen (urine)[f]	X							
Breath Alcohol[g]	X							
Urine Pregnancy Test for Females[h]	X			X	X	X	X	X
Plasma Sample for biobank[i]	X			X	X	X	X	X
OPTIONAL LABORATORY TESTING								
SARS-CoV-2 PCR test[j]	X			X	X	X	X	
Drug Screen (urine)[f]				X	X	X	X	X
Breath Alcohol[g]				X	X	X	X	X
Serum Pregnancy Test (b-HCG)[h]	X			X	X	X	X	X
PK Blood Sampling[k]	X			X	X	X	X	
SCALE ASSESSMENTS								
MADRS10	X			X	X	X	X	X
CGI-S[l]	X			X	X	X	X	X
CGI-I[l]				X	X	X	X	X
HAM-A	X			X	X	X	X	X
HCRU (ER/re-hospitalization due to MDD)	X				X		X	X
C-SSRS[m]	X			X	X	X	X	X
CADSS	X			X	X	X	X	
Global COVID-19 Impact Assessment	X				X		X	
PATIENT REPORTED OUTCOMES								
SDQ	X				X		X	
SDS	X				X		X	
PROMIS™-SD	X				X		X	
DSST[n]	X				X		X	
PDQ-D-5	X				X		X	
TSQM	X				X		X	
SF-12v2	X				X		X	
EuroQol EQ-5D-5L	X				X		X	
WPAI:SHP	X				X		X	
ASEX	X				X		X	
DOSING								
Study Drug Dispensing	X		X	X	X	X		
Study Drug Return/ Compliance/ Accountability[o]			X	X	X	X	X	
Dosing eDiary Compliance[p]	X	X	X	X	X	X	X	
AEs	X	X	X	X	X	X	X	X
MADDERS[q]	X	X	X	X	X	X	X	
MADDERS Medication Use Survey[q]							X	X

De Novo Participants

Main Study Visit*	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
	Screening	**OLS Baseline Day 1**							**EOT/ET Day 365**	**EOS[a] Follow-up**
Telephone Contact**				**At 2-week (±2 d) intervals from previous month's assessment**						
Assessment Month***	**Up to -30 days******	**0**	**D7 (±2d)**	**1 (±5d)**	**2 (±5d)**	**3 (±5d)**	**6 (±5d)**	**9 (±5d)**	**12 (±5d)**	**13 (±5d)**
Informed Consent	X									
Medical History	X									
Psychiatric History	X									
Medication History	X									
Demographics and Height	X									
Inclusion/Exclusion Review	X	X								
Physical Examination [b]	X	X[b]					X[b]		X[b]	X[b]
Weight and BMI	X	X				X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Vital Signs (including body temperature) and Pulse Oximetry[c]	X	X	X	X	X	X	X	X	X	X
ECG[d]	X	X[d]	X[d]	X[d]	X	X	X		X	X
LABORATORY TESTING										
Hematology	X	X				X	X	X	X	X
Biochemistry[e]	X	X[e]				X	X	X	X[e]	X
Urinalysis	X	X				X	X	X	X	X
Hepatitis B, Hepatitis C, and HIV	X									
TSH	X									
Drug Screen (urine) [f]	X	X[f]								
Breath Alcohol [g]	X	X								
Serum FSH and b-HCG Test for Females	X									
Urine Pregnancy Test for Females[h]	X	X				X	X	X	X	X
Plasma Sample for biobank[i]		X				X	X	X	X	X
PK Blood Sampling [j]		X	X	X						
OPTIONAL LABORATORY TESTING										
Blood Sample for DNA Extraction[k]		X								
SARS-CoV-2 PCR test[l]	X	X				X	X	X	X	
Drug Screen (urine) [f]						X	X	X	X	X
Breath Alcohol [g]						X	X	X	X	X
Serum Pregnancy Test (b-HCG)[h]		X				X	X	X	X	X
PK Blood Sampling [j]		X	X	X	X	X	X	X	X	
SCALE ASSESSMENTS										
SAFER Interview	X[m]									
ATRQ	X[m]									
MADRS10		X	X	X		X	X	X	X	X
SCID-5 MDD	X									
HAMD17	X	X								
CGI-S [n]		X	X	X		X	X	X	X	X
CGI-I [n]			X	X		X	X	X	X	X
HAM-A		X	X	X		X	X	X	X	X
HCRU (ER/re-hospitalization due to MDD)		X					X		X	X
C-SSRS[o]	X	X	X	X	X	X	X	X	X	X
CADSS		X	X	X	X	X	X	X	X	
Global COVID-19 Impact Assessment		X					X		X	
PATIENT REPORTED OUTCOMES										
SDQ		X					X		X	
SDS		X					X		X	
PROMIS™-SD		X					X		X	
DSST [p]		X					X		X	
PDQ-D-5		X					X		X	
TSQM		X[q]					X		X	
SF-12v2		X					X		X	
EuroQol EQ-5D-5L		X					X		X	
WPAI:SHP		X					X		X	
ASEX		X					X		X	
DOSING										
Study Drug Dispensing		X[r]	X	X	X	X	X	X		

Supplementary Figure 1. MADRS10 response and remission rates by treatment group





Supplementary Table 3. Summary of Completed Esmethadone Studies

Esmethadone Clinical Program: Overview

Study Number and Status	Design	Number of Subjects	Study Title	Treatment and Duration
Phase 1 Studies				
REL-1017-111 Completed	Phase 1, double-blind, randomized, placebo-controlled	42 healthy subjects (31 REL-1017 11 placebo)	Phase 1 Study to Investigate the Safety, Tolerability, and Pharmacokinetic Profile of Single Ascending Doses of d-Methadone in Healthy Subjects	42 subjects were randomly assigned to the treatment phase, with 8 subjects assigned to each cohort of 5, 20, 60, 100, and 150 mg (2 subjects to placebo, 6 subjects to REL-1017) and 2 subjects assigned to the 200 mg cohort (1 subject to placebo, 1 subject to REL-1017) (Bernstein 2019).
REL-1017-112 Completed	Phase 1, double-blind, randomized, placebo-controlled	24 healthy subjects (18 REL-1017 6 placebo)	Phase 1 Study to Investigate the Safety, Tolerability, and Pharmacokinetic Profile of Multiple Ascending Doses of d-Methadone in Healthy Subjects	24 healthy subjects were randomized into 3 arms of 25, 50, and 75 mg REL-1017. In each arm, 2 subjects were dosed with placebo and 6 with REL-1017 from Day 1 to Day 10 (Bernstein 2019).
REL-1017-113 Completed	Phase 1, open-label, fixed-sequence, single-dose and multiple-dose, drug-drug interaction study	28 healthy subjects	Phase 1, Drug-Drug Interaction Study to Evaluate the Effects of REL-1017 on the Pharmacokinetics of Dextromethorphan and Midazolam in Healthy Subjects	Day 1: single dose of 2 mg midazolam. Day 2: single dose of 30 mg dextromethorphan. 48 h washout period Day 4: single 75 mg loading dose REL-1017 in combination with a single dose of 30 mg dextromethorphan. Days 6 to 18: 25 mg of REL-1017 once daily (Q.D.). Day 19: 25 mg REL-1017 co-administrated with a single dose of 2 mg midazolam (Ferri 2023).
REL-1017-114 Completed	Phase 1, open-label, fixed-sequence, single-dose and multiple-dose, drug-drug interaction study	28 healthy subjects	A Single Center, Open-label, Drug-Drug Interaction Study to Assess the Effect of Cobicistat on the Pharmacokinetic Profile of REL-1017 in Healthy Subjects	Day 1: REL-1017 25 mg single dose. Days 11-20: Cobicistat 150 mg QD. Day 15: Cobicistat 150 mg followed by administration of REL-1017 25 mg within ≤2 minutes (Ferri 2023).

Esmethadone Clinical Program: Overview

Study Number and Status	Design	Number of Subjects	Study Title	Treatment and Duration
REL-1017-117 Completed	Phase 1, open-label, single-dose, parallel study	40 adult subjects with mild, moderate, sever renal impairment and end stage renal disease	A Phase 1, Open-Label, Single-Dose, Parallel-Group Study to Evaluate the Effects of Renal Impairment on the Pharmacokinetics of REL-1017	Subjects will receive a single oral dose of 25 mg REL-1017 on Day 1 (Ferri 2024).
REL-1017-118 Completed	Phase 1, open-label, single-dose, parallel study	27 adult subjects with mild or moderate hepatic impairment	A Phase 1, Open-Label, Single-Dose, Parallel-Group Study to Evaluate the Effects of Hepatic Impairment on the Pharmacokinetics of REL-1017	Subjects will receive a single oral dose of 25 mg REL-1017 on Day 1 (Ferri 2024).
REL-1017-121 Completed	Phase 1, open-label, single-dose study	8 healthy subjects	A Phase 1, Open-label Study of the Absorption, Metabolism, and Excretion of [14C]-REL-1017 Following a Single Oral Dose in Healthy Male Subjects	Single Dose of 25 mg C-14 labeled REL-1017 on Day 1 (Ferri 2023).
REL-1017-124 Completed	Randomized, double-blind, active- and placebo-controlled crossover	47 recreational drug users with opioid experience (Note: 44 subjects were included in the Modified Completer Population Analysis)	A Randomized, Double-Blind, Active- and Placebo-Controlled Crossover Study to Assess the Abuse Potential of REL-1017 Relative to Oxycodone and Placebo in Healthy Experienced Recreational Drug Users	In the Treatment Phase, each subject was randomized to receive the following treatments (one in each treatment period) in a double-blind, double-dummy crossover fashion: 25, 75, and 150 mg REL-1017, 40 mg oxycodone, and placebo (Shram 2022).
REL-1017-126 Completed	Randomized, double-blind, triple-dummy, active- and placebo-controlled crossover	51 recreational drug users with ketamine experience (Note: 50 subjects were included in the Modified Completer Population Analysis)	A Randomized, Double-Blind, Triple-Dummy, Active- And Placebo-Controlled Crossover Study to Assess the Abuse Potential of REL-1017 Relative to Intravenous Ketamine and Placebo in Healthy Experienced Recreational Drug Users. Dextromethorphan 300 mg was also administered as an exploratory endpoint.	In the Treatment Phase, each subject was randomized to receive the following treatments (one in each treatment period) in a double-blind, triple-dummy crossover fashion: 25, 75, and 150 mg REL-1017, ketamine 0.5 mg/kg IV over 40 minutes, dextromethorphan (DXM) 300 mg, and IV and oral placebo (Shram 2022).
Phase 2 Study				

Esmethadone Clinical Program: Overview

Study Number and Status	Design	Number of Subjects	Study Title	Treatment and Duration
REL-1017-202 Completed	Phase 2, double-blind, randomized, placebo-controlled	62 adults with MDD (40 REL-1017 22 placebo)	Phase 2a, Multicenter, Randomized, Double-Blind, Placebo-Controlled, 3-Arm Study to Assess the Safety, Tolerability, P.K. Profile, and Symptom Response of a 7-Day Dosing with REL-1017 25 mg once daily (Q.D.) and 50 mg Q.D. as Adjunctive Therapy in the Treatment of patients Diagnosed with Major Depressive Disorder	62 adults with MDD diagnosed with a current MDE with inadequate response to one to three courses of antidepressant treatment; 19 patients received REL-1017, 25 mg treatment (75 mg loading dose on Day 1), 21 patients received REL-1017, 50 mg treatment (100 mg loading dose on Day 1), and 22 patients received placebo. Treatment duration: 7 days. This study showed safety and efficacy at both tested doses (Fava 2022).
Phase 3 Studies				
REL-1017-301 Completed	Phase 3, randomized, double-blind, placebo-controlled	227 adults with MDD	Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of REL-1017 in Patients with Major Depressive Disorder and Inadequate Response to Ongoing Antidepressant Treatment	Adults with MDD diagnosed with a current MDE with inadequate response to ongoing antidepressant treatment. Patients are randomized in a 1:1 ratio to the active REL-1017 25 mg arm or placebo arm. On the first day a loading dose of three tablets (75 mg REL-1017 or placebo) is administered. Treatment duration: 28 days. This study did not meet its primary endpoint. Encouraging post-hoc results were seen in the subgroup of patients with severe depression (Fava 2024).
REL-1017-303 Completed	Phase 3, randomized, double-blind, placebo-controlled	232 adults with MDD	A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of REL-1017 Monotherapy for Major Depressive Disorder	Adults with MDD diagnosed with a current MDE. Patients were randomized in a 1:1 ratio to the active REL-1017 25 mg or placebo arm. On the first day a loading dose of three tablets (75 mg REL-1017 or placebo) was administered. Treatment duration: 28 days. This study did not meet its primary endpoint.

ADT = antidepressant therapy; IND = Investigational New Drug; MDD = major depressive disorder; MDE = major depressive episode; OLS = open-label study; Q.D. = once daily.

Summary of Completed Phase 2 and 3 Studies with Esmethadone

REL-1017-202 Study: A 7-day, Phase 2, multicenter, randomized, double-blind, placebo-controlled inpatient trial evaluated the safety, tolerability, and efficacy of esmethadone 25 mg or 50 mg or placebo in patients with MDD and inadequate response to previous antidepressants (Fava et al, 2022). The improvement in MADRS score shown on day 4 in both of the REL-1017 dosage groups was sustained through day 7 (last dose) and day 14 (7 days after the last dose), with effect sizes from 0.7 to 1.0. This trial showed favorable safety, tolerability, and pharmacokinetic profiles and suggests that REL- 1017 may have rapid and sustained antidepressant effects compared with placebo in patients with inadequate responses to antidepressant treatments (Fava 2022).

REL-1017-301 Study (RELIANCE I) (NCT04688164) evaluated esmethadone vs. placebo as adjunctive therapy in 227 patients with MDD and inadequate response to antidepressants. In the ITT analysis, mean change from baseline for the MADRS was -15.1 with esmethadone and -12.9 with placebo (mean difference = 2.3; p=0.154; Cohen's effect size 0.21). In a per protocol analysis (n=198): mean change from baseline for the MADRS was -15.6 for esmethadone and -12.5 for placebo (mean difference: 3.1; p=0.051, effect size: 0.29). Post-hoc analyses in patients with a baseline MADRS $\geq$35 in the ITT population reported a mean difference of 6.9 (p=0.0059, effect size=0.57; and in the per protocol population a mean difference of 7.9 (p=0.0015, effect size=0.69). Adverse events were predominantly mild or moderate and transient, with no significant differences between groups and no opioid-like effects, no psychotomimetic effects, no withdrawal effects and no adverse events related to QTcF prolongation (Fava 2024).

REL-1017-303 Study (RELIANCE III study; NCT05081167) evaluated esmethadone as monotherapy for MDD in 232 patients with MDD. The study did not achieve its primary endpoint (results posted on clinicaltrials.org). The mean reduction in the MADRS score at Day 28 was 14.8 points with esmethadone and 13.9 points with placebo. Adverse events were predominantly mild or moderate and transient, with no significant differences between groups and no opioid-like effects, no psychotomimetic effects, no withdrawal effects and no adverse events related to QTcF prolongation.