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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

**Authors:** Maurizio Fava, MD; Luca Pani, MD; Sara De Martin, PhD; Andrew J Cutler, MD; Charles W. Gorodetzky, MD, PhD; Frank J. Vocci, PhD; Frank L. Sapienza, MS; Thomas R. Kosten, MD; Cornelia Kröger, PhD; Paggard Champasa, PhD; Clotilde Guidetti, MD; Stefano Comai, PhD; Andrea Mattarei, PhD; Franco Folli, MD; David Bushnell, MS; Sergio Traversa, PharmD; Charles E. Inturrisi, PhD; Paolo L. Manfredi, MD; and Marco Pappagallo, MD

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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<br>(Maximum allowed dose 40 mg QD) |
| escitalopram | 10 mg QD<br>(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

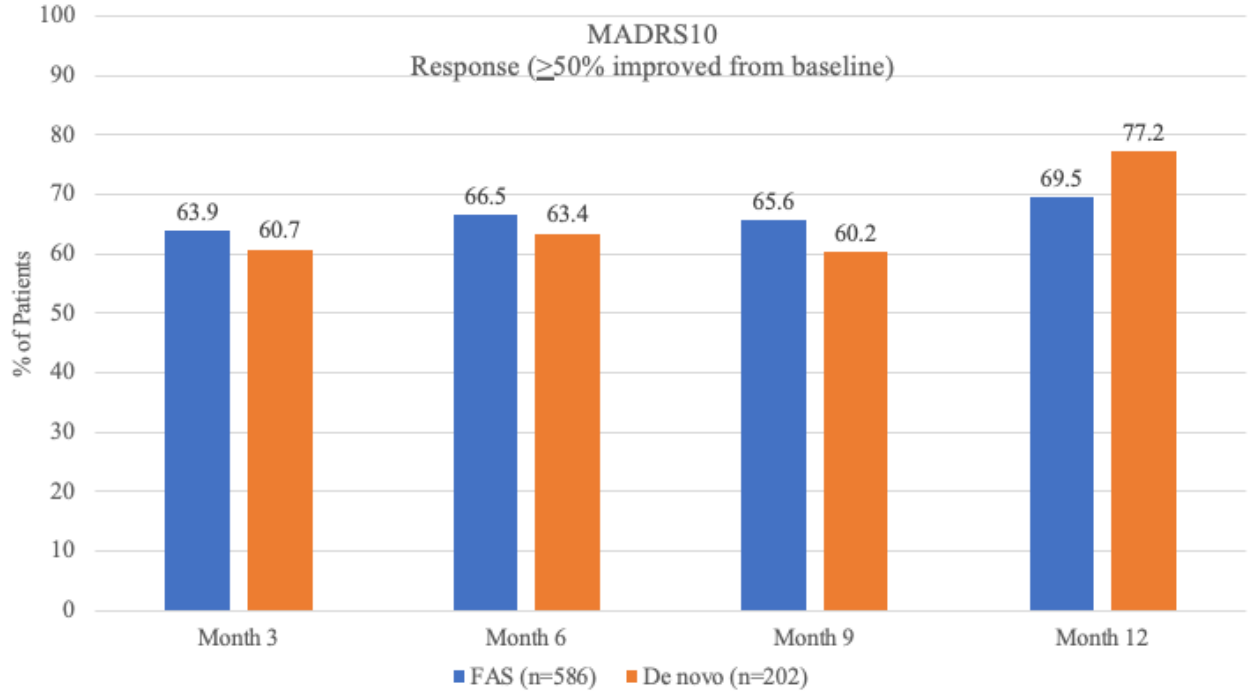
*Rollover* Participants

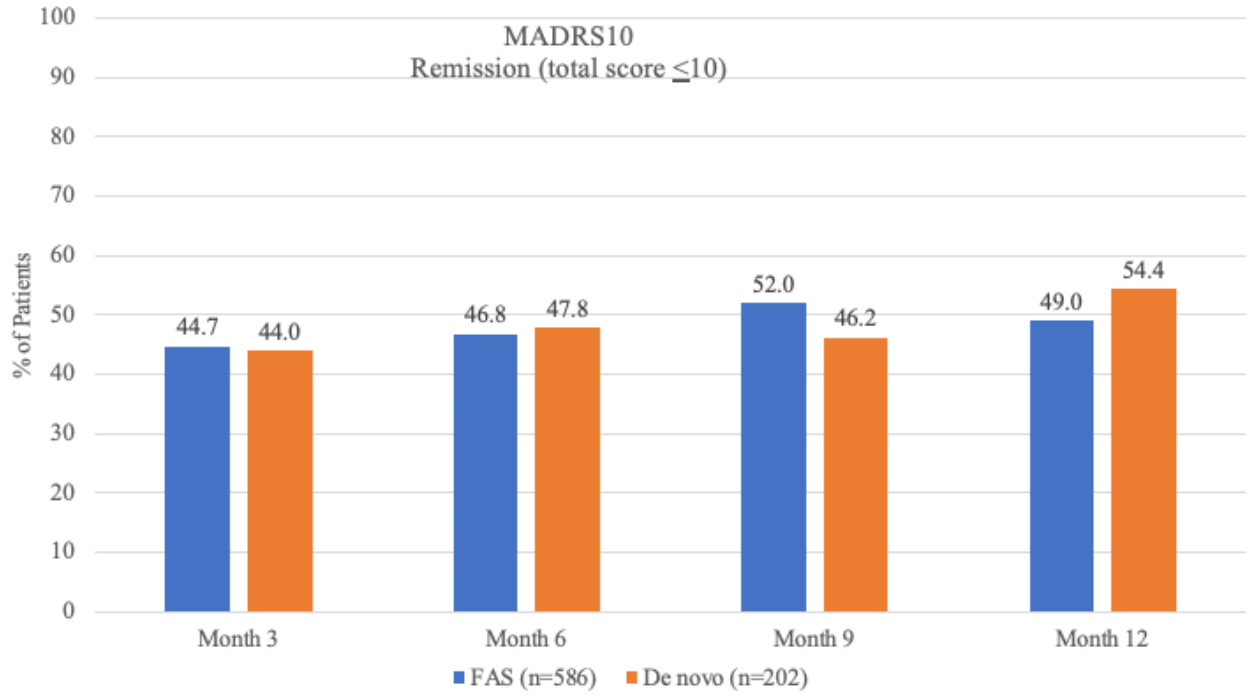
| **Main Study Visit*** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** |
|---|---|---|---|---|---|---|---|---|
| | **OLS Baseline Day 1†** | | | | | | **EOT/ET Day 365** | **EOS[a] Follow-up** |
| **Telephone Contact**** | | **At 2-week (±2 days) intervals from previous month's visit** | | | | | | |
| **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<br>Completed | Phase 1, double-blind, randomized, placebo-controlled | 42 healthy subjects<br>(31 REL-1017<br>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<br>Completed | Phase 1, double-blind, randomized, placebo-controlled | 24 healthy subjects<br>(18 REL-1017<br>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<br>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.<br>Day 2: single dose of 30 mg dextromethorphan.<br>48 h washout period<br>Day 4: single 75 mg loading dose REL-1017 in combination with a single dose of 30 mg dextromethorphan.<br>Days 6 to 18: 25 mg of REL-1017 once daily (Q.D.).<br>Day 19: 25 mg REL-1017 co-administrated with a single dose of 2 mg midazolam (Ferri 2023). |
| REL-1017-114<br>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.<br>Days 11-20: Cobicistat 150 mg QD.<br>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<br>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<br>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<br>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<br>Completed | Randomized, double-blind, active- and placebo-controlled crossover | 47 recreational drug users with opioid experience<br>(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<br>Completed | Randomized, double-blind, triple-dummy, active- and placebo-controlled crossover | 51 recreational drug users with ketamine experience<br>(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.<br>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<br>Completed | Phase 2, double-blind, randomized, placebo-controlled | 62 adults with MDD<br>(40 REL-1017<br>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.<br>This study showed safety and efficacy at both tested doses (Fava 2022). |
| **Phase 3 Studies** | | | | |
| REL-1017-301<br>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<br>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.