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

Poster #79

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INTRODUCTION

- Major depressive disorder (MDD) is a leading cause of disability and disease burden in the United States.[1]
- In 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]
- 50%–60% of patients with MDD fail to achieve an adequate response following treatment with an antidepressant.[3]
- Esmethadone 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.[4,5]
- Current literature indicates that NMDAR uncompetitive antagonists, including esmethadone (REL-1017), are at the forefront among novel antidepressant candidates.[6,7]
- As adjunctive treatment of MDD, esmethadone demonstrated efficacy and safety in clinical studies.[8-10]

OBJECTIVE

Evaluate the long-term safety and tolerability, as well as the long-term durability of the antidepressant effects of esmethadone (registered at clinicaltrials.gov: NCT04855760).

METHODS

Study Design:

- Multicenter, open-label, long-term study of esmethadone in MDD patients.
- Patients completing randomized, double-blind Phase 3 trials (NCT04688164, NCT04855747, NCT05081167) of esmethadone as adjunctive therapy continued esmethadone 25 mg daily for up to 1 year.
- *De novo* patients also were enrolled with a 75 mg loading dose of esmethadone on Day 1 and then 25 mg daily for the remainder of the study (Days 2-365).
- For *de novo* participants, eligibility was assessed based on inclusion/exclusion criteria assessed by the investigator, and independently verified by a MGH-CTNI-certified clinician using the SAFER/Antidepressant Treatment Response Questionnaire. Rollover patients were eligible based on participation in double blind placebo controlled esmethadone trials.

Study Assessments:

- Safety was assessed with physical exam, vital signs, clinical laboratory testing, recording of treatment emergent adverse events (TEAE) and safety assessments: Columbia Suicide Severity Rating Scale (C-SSRS); Clinician-Administered Dissociative States Scale (CADSS); The Misuse, Abuse, and Diversion Drug Event Reporting System (MADDERS); The Arizona Sexual Experience Scale (ASEX)
- Efficacy assessments included (Montgomery and Asberg Depression Rating Scale (MADRS10); Clinical Global Impression and Severity scales (CGI-I and CGI-S); Hamilton Anxiety Rating Scale (HAM-A); Symptoms of Depression Questionnaire (SDQ); Self-Rating Depression Scale (SDS); Patient-Reported Outcomes Measurement Information System (PROMIS™) Sleep Disturbance (PROMIS-SD); Digit symbol substitution test (DSST); Perceived Deficits Questionnaire for Depression (PDQ-D-5) – cognition scale; (Treatment Satisfaction Questionnaire for Medication) (TSQM); Short Form Health Survey (SF-12); EuroQol 5-Dimension (EQ-5D-5L); Work Productivity and Activity Impairment Questionnaire (WPAI:SHP); The Arizona Sexual Experience Scale (ASEX).

Data Analysis:

- The Safety Set included all participants who received ≥1 dose of study drug.
- The Full Analysis Set (FAS) comprised all participants who received ≥1 dose of study drug and had ≥1 post-baseline efficacy assessment.
- Data were reported using descriptive statistics.

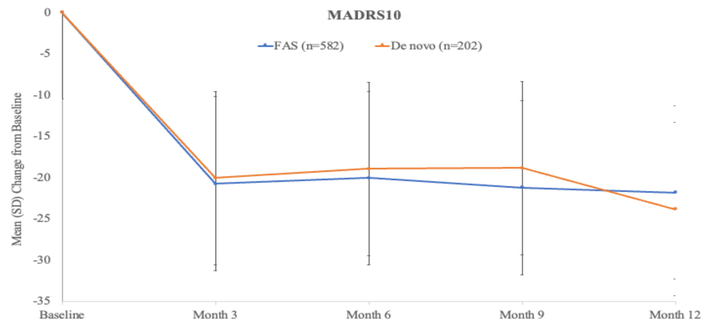
RESULTS

Table 1. Baseline characteristics (Safety Population)

Characteristics	Patients (n=618)
Age, years [a]	42.9 ± 13.5
Body mass index. kg/m^2 [a]	27.8 ± 4.3
Body weight, kg [a]	79.1 ± 16.3
Female, n (%)	428 (69.3)
Hispanic or Latino	162 (26.2)
Race	
Black or African American	95 (15.4)
Caucasian	469 (75.9)
Other	54 (8.7)
Time since diagnosis of MDD, years [a]	15.6 ± 11.4
Age MDD began impacting function, years [a]	25.9 ± 13.6
Number of lifetime depressive episodes [a]	6.7 ± 9.1
Number of depressive episodes in past 5 years [a]	2.3 ± 1.7
Duration of current major depressive episode, years [a]	1.0 ± 1.4

[a] Mean ± standard deviation

Figure 1. Mean Change from Baseline for MADRS10 Over Time (FAS Population)

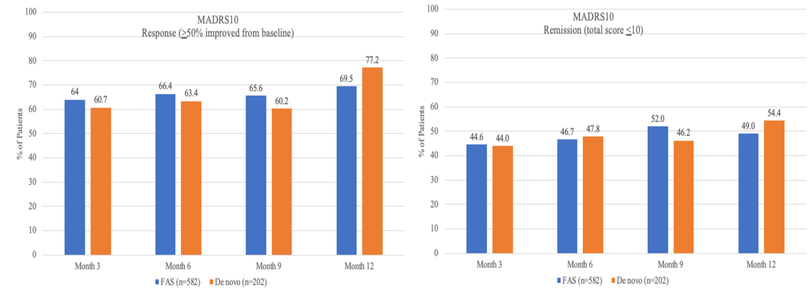


- Mean MADRS10 total score decreased from baseline to month 3 by approximately 20 points and the CFB was sustained through month 12 (Figure 1).
- For the MADRS 10, response rates at 3 and 12 months were 64.0% and 69.5%, and remission rates at month 3 and month 12 were 44.6% and 49.0%, respectively (Figure 2).
- CGI-S score decreased from 4.8 (0.7) at baseline to 2.5 (1.2) at month 12
- HAM-A score decreased from baseline of 20.4 (5.8) to 9.1 (7.1)
- CGI-I scores at 12 months were improved (score of <3) in 89.4%
- Results were similar in the FAS and in de novo patients
- MADRS10;CGI-S, CGI-I; HAM-A, PROMIS-SD, DSST, PDQ-D5, TSQM, SF-12v2, EQ-5D-5L, WPAI-SHP, ASEX, SDQ, and SDS showed improvement in both FAS and de novo populations

CONCLUSIONS

- In this open-label trial, esmethadone for 1 year was safe and well-tolerated, consistent with results observed in other esmethadone trials.[8-10]
- No meaningful safety signal was observed for weight gain, sexual dysfunction, cardiovascular, neurological or dissociative effects, withdrawal phenomena or abuse liability.
- Antidepressant effects were robust and durable with high rates of response and remission
- Overall, the results are consistent with previous clinical studies of esmethadone 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.

Figure 2. MADRS10 Response and Remission Rates in the FAS Population and De Novo Population



Safety/Tolerability

- ≥1treatment-emergent adverse event (TEAE) was reported by 347 (56.1%) patients, and ≥1 treatment-related TEAE was reported by 168 (27.2%) patients (**Table 2**).
- Mean (SD) CADSS scores were 0.6 (2.2) at baseline declining to 0.2 (0.9) at month 12, a change from baseline of -0.6 (2.9).
- 57 MADDERS cases were identified and adjudicated in 49 patients. No cases were classified as “abuse”. Two cases were classified as “misuse”: both patients were re-directed to take medication as prescribed and continued in the trial without further issues.

Table 2. Treatment-Emergent Adverse* Events and Treatment-Related Adverse Events**

Safety Population (N=618)	Number (%)
At least one TEAE	347 (56.1)
At least one treatment-related TEAE	168 (27.2)
At least one serious TEAE	7 (1.1)
At least one serious treatment-related TEAE	0
TEAE leading to study discontinuation	36 (5.8)
Treatment-related TEAE leading to discontinuation	21 (3.4)
TEAE occuring in at least 5% of patients	
COVID-19	60 (9.7)
Headache	60 (9.7)
Upper respiratory infection	53 (8.6)
Nausea	31 (5.0)
Most common treatment-related TEAE	
Headache	27 (4.4)
Nausea	25 (4.0)
Dizziness	15 (2.4)

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DISCLOSURES

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