Efficacy and Safety of Esmethadone (REL-1017) in Patients With Major Depressive Disorder and Inadequate Response to Standard Antidepressants: A Phase 3 Randomized Placebo-Controlled Trial

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INTRODUCTION

- Approximately 50% to 60% of patients with major depressive disorder (MDD) do not obtain an adequate response following their first antidepressant treatment.
- Severe depression, defined as a Montgomery-Åsberg Depression Rating Scale (MADRS) total score ≥35, may negatively impact functional outcomes.
- Antidepressant tolerance/tachyphylaxis (AT), defined as an initial response to antidepressant treatment followed by relapse or no response, is a poor prognostic indicator for subsequent antidepressant treatment.
- Esmethadone (REL-1017) has demonstrated promise as a safe and well-tolerated oral, once-daily, uncompetitive N-methyl-D-aspartate receptor (NMDAR) antagonist with potential efficacy as an adjunctive treatment of MDD.

AIM

- To evaluate the efficacy, safety, and tolerability of REL-1017 as an adjunctive treatment in patients with MDD, in a subgroup with AT (independently assessed at screening, prior to randomization), and in a subgroup with severe depression.

METHODS

Study Design:
- A Phase 3, double-blind, randomized, placebo-controlled trial of oral once-daily adjunctive REL-1017 was conducted in adult outpatients with MDD and inadequate response to 1 to 3 antidepressants administered at adequate therapeutic doses and for at least 8 weeks.

- Patients were aged 18 to 70 years, inclusive, and had a history of ≥12 weeks or more of treatment with an antidepressant and experienced a recurrence of depressive symptoms.

- Exclusion criteria included any condition that could interfere with the ability to take the study medication or complete the study.

- The study was conducted at 37 clinical sites in 5 countries.

Endpoint Measurements:
- The primary efficacy endpoint was the absolute change from baseline to Day 28 in the MADRS total score.
- The primary safety endpoint was the incidence of adverse events (AEs) occurring in 5% or more of patients per treatment arm.

DISCUSSIONS

Dr. Pappagallo and Mannedta contributed equally. This work was funded by Reimeda Therapeutics, Inc. Drs. De Martin, Guidetti, Alimonti, and Mannedta are employed by or have received compensation from companies or institutions that received funding from Reimeda Therapeutics, Inc. Dr. Fava is a consultant to Reimeda Therapeutics, Inc. and has received honoraria for speaking engagements. Dr. Stahl, Paro, Gorodetzky, Vocci, Sapienza, Kost, and Mannedta: Pappagallo and Intral have received consultant fees from Reimeda Therapeutics, Inc. Dr. De Martin and Mannedta have received grant support from MGH LLC and consultant fees from Neurorobot LLC. Drs. Guidetti and Comai have received consultant fees from MSGM LLC. Drs. Intral, Mannedta, and Intral are co-inventors of technology related to esmethadone.

RESULTS

Table 1. MADRS total score change from baseline at Day 28.

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Placebo-Controlled ITT N=227</th>
<th>REL-1017 N=198</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo mean (SD)</td>
<td>9.7 (11.0)</td>
<td>17.5 (10.4)</td>
</tr>
<tr>
<td>REL-1017 mean (SD)</td>
<td>17.5 (10.4)</td>
<td>16.9 (11.3)</td>
</tr>
<tr>
<td>REL-1017 vs placebo MD (SD)</td>
<td>2.3 (8.6)</td>
<td>2.5 (7.5)</td>
</tr>
</tbody>
</table>

- In the ITT population, there was a statistically significant mean difference of 2.3 (95% confidence interval [CI] 0.3–4.3, P = 0.0215) in the MADRS total score change from baseline to Day 28 in the REL-1017 group compared with the placebo group.
- The MADRS total score change from baseline to Day 28 in the REL-1017 group was 2.3 (95% CI 0.3–4.3, P = 0.0215), whereas in the placebo group, it was 7.5 (95% CI 5.2–9.8, P < 0.001).

Table 2. Treatment-emergent adverse events (TEAEs), safety set (N=227).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo-Controlled N=227</th>
<th>REL-1017 N=198</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Total</td>
<td>% Total</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>9 (7.9)</td>
<td>11 (5.6)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4 (3.5)</td>
<td>4 (2.0)</td>
</tr>
<tr>
<td>Constipation</td>
<td>6 (5.3)</td>
<td>7 (3.6)</td>
</tr>
</tbody>
</table>

- There were no statistically significant differences between the REL-1017 and placebo groups in the incidence of TEAEs occurring in 5% or more of patients per treatment arm.

Table 3. Baseline demographic characteristics, safety set (N=227).

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Placebo-Controlled N=227</th>
<th>REL-1017 N=198</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>46.7 (11.2)</td>
<td>46.6 (11.3)</td>
<td>0.960</td>
</tr>
<tr>
<td>Gender</td>
<td>55 (24.4)</td>
<td>52 (26.2)</td>
<td>0.517</td>
</tr>
<tr>
<td>Race</td>
<td>77.1 (77.1)</td>
<td>77.2 (77.3)</td>
<td>0.969</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>54.8 (54.8)</td>
<td>54.8 (54.8)</td>
<td>0.960</td>
</tr>
<tr>
<td>Gender</td>
<td>55 (24.4)</td>
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- There were no statistically significant differences between the REL-1017 and placebo groups in the incidence of TEAEs occurring in 5% or more of patients per treatment arm.

CONCLUSIONS

- The efficacy of REL-1017 was considerably more favorable in the prespecified analysis compared to the ITT analysis.
- Although discrepancies in outcomes between ITT and PP populations are typically related to adherence, in this study, differences were not the result of tolerability and safety adverse events affecting treatment compliance.
- Professional patients avoided more frequently the response to a potential antidepressant with no detectable psychoactive effects.
- We hypothesized that the ITT population may have contained a higher proportion of "professional patients" and patients with transient reactive depression (perhaps related to COVID-19 pandemic stress) who were poorly motivated to complete treatment and assessments.
- The more favorable prespecified efficacy outcomes observed in females and in subjects ≤50 years of age who could suggest heightened REL-1017 effectiveness in these populations. Alternatively, these subgroups may have reduced likelihood of including "professional patients"; professional patients are more likely to be younger males.
- Favorable outcomes were observed in post hoc analyses of PP AT and MADRS 235 endpoints.
- The MDD history in the AT subgroup may have been better substantiated due to the careful assessment performed by the independent group of specialized MGH CTN clinicians and the use of the validated MGH ATRQ screening tool.
- The MGH ATRQ selection of AT patients may have aided in screening out "professional patients" and patients with transient reactive depression, leading to a lower proportion of such patients in the AT subgroup.

- The favorable efficacy outcomes observed in the AT subgroup also raised the interesting hypothesis that REL-1017 may have efficacy toward mitigating antidepressant tolerance, with a mechanism that is potentially mediated by NMDAR competitive antagonism.
- The 235 baseline MADRS subgroup may have included a lower proportion of "professional patients" and patients with transient reactive depression.
- REL-1017 may be a safe and effective adjunctive treatment for patients with MDD, including patients with severe MDD or at higher risk for treatment failure because of AT, with an AE profile that is likely comparable to currently available MDD treatments.
- In MDD trials assessing drugs with favorable adverse event profiles, the PP analysis may provide a superior measure for evaluating efficacy compared to the ITT analysis.

REFERENCES