P.0165

Efficacy of Esmethadone (REL-1017) in Patients With Major Depressive Disorder and Antidepressant Tolerance (Antidepressant Tachyphylaxis)

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INTRODUCTION

- 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 adjunctive treatment of major depressive disorder (MDD) [1-3]
- It is estimated that more than 50% of patients with MDD may develop a tolerance to antidepressant treatments called antidepressant tachyphylaxis (AT), wherein an initial treatment response is followed by a relapse during maintenance treatment with the same antidepressant [4]

AIM

- To evaluate the efficacy and tolerability of REL-1017 in patients with MDD and in a subgroup with AT independently assessed at screening, prior to randomization

METHODS

Study Design:

- A Phase 3, randomized, double-blind, placebo-controlled trial of oral once-daily adjunctive REL-1017 enrolled patients with MDD who had shown an inadequate response to 1 to 3 antidepressants during the current major depressive episode (MDE)
- Patients were 18 to 65 years old and randomly assigned to receive REL-1017 (75 mg loading dose on Day 1 and then 25 mg/day thereafter) or placebo for 28 days
- During screening (prior to randomization), patients' previous antidepressant treatment response and AT were independently assessed by clinicians from the Massachusetts General Hospital Clinical Trials Network and Institute (MGH-CTNI) using the MGH Antidepressant Treatment Response Questionnaire (ATRQ) [5]

Endpoint Measurements:

- The efficacy endpoint was the absolute change from baseline to Day 28 in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score
- One of the key secondary endpoints was response rate, defined as the percentage of patients with ≥50% decrease in MADRS total score from baseline at Day 28

Data Analysis:

- The following analysis sets were included:
  - Intent-to-treat (ITT) population: all randomized patients
  - In this study, the ITT population was the same as the full analysis set (FAS) and the safety set (SS); all randomized patients also received at least 1 dose of study drug
  - Per-protocol (PP) population: patients who completed treatment with no major protocol deviations impacting efficacy assessments
  - AT subgroups: patients with AT from ITT and PP populations
- Data for the primary efficacy endpoint were analyzed using mean difference (MD) in MADRS total score
- Data for response rate were analyzed using a chi-square test (2-sided with α=0.05)

RESULTS

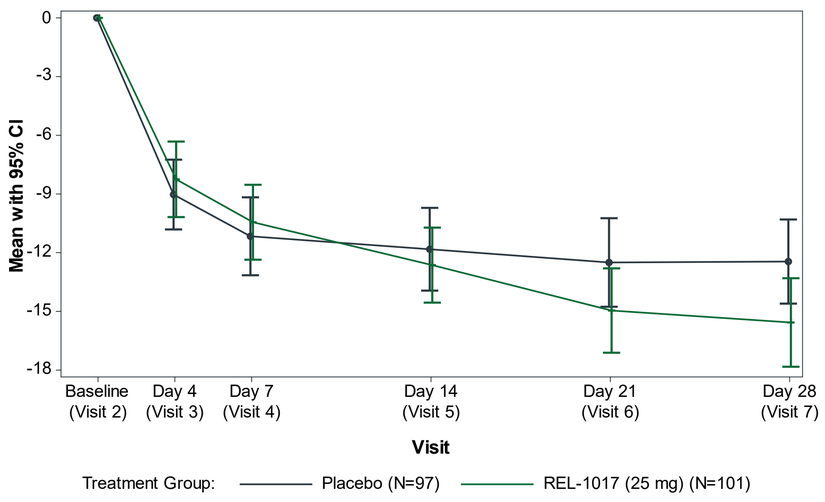

Figure 1. MADRS total score change from baseline, PP (N=198). At Day 28, the MD between REL-1017 (N=101) and placebo (N=97) was 3.1 (*P*=0.0510; effect size=0.29).

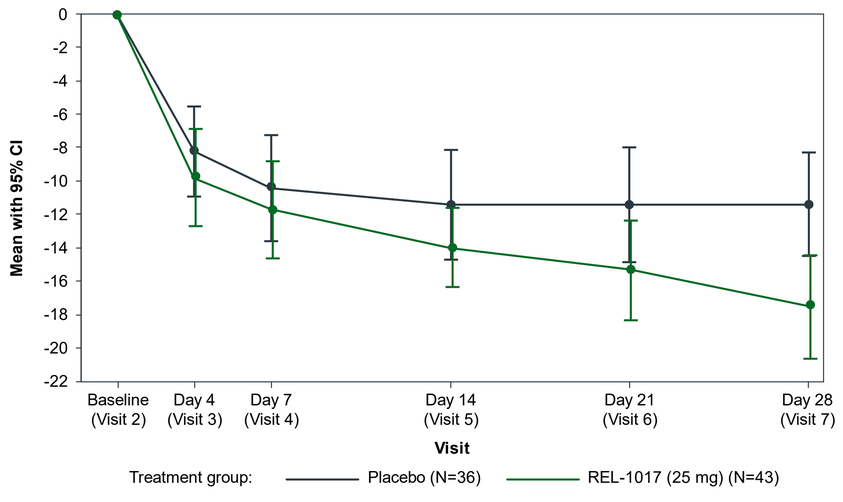

Figure 2. MADRS total score change from baseline, PP AT (N=79). At Day 28, the MD between REL-1017 (N=43) and placebo (N=36) was 6.1 (*P*=0.0101; effect size=0.62).

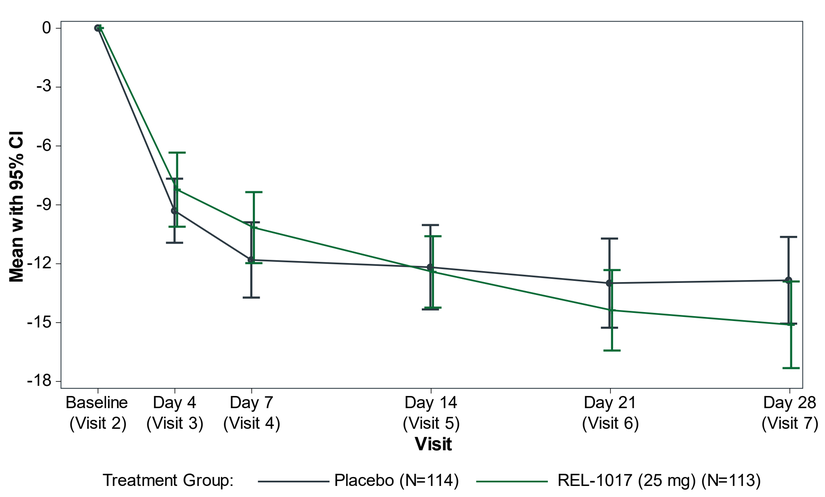

Figure 3. MADRS total score change from baseline, ITT (N=227). At Day 28, the MD between REL-1017 (N=113) and placebo (N=114) was 2.3 (*P*=0.1537; effect size=0.21).

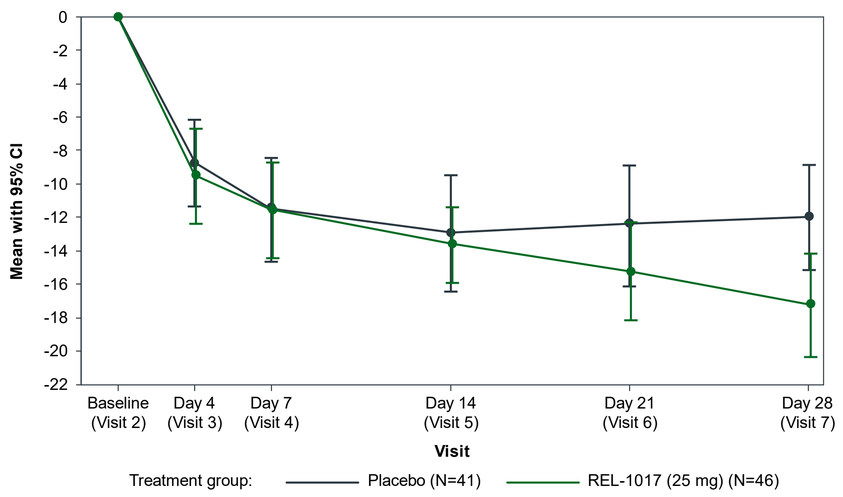

Figure 4. MADRS total score change from baseline, ITT AT (N=87). At Day 28, the MD between REL-1017 (N=46) and placebo (N=41) was 5.4 (*P*=0.0232; effect size=0.53).

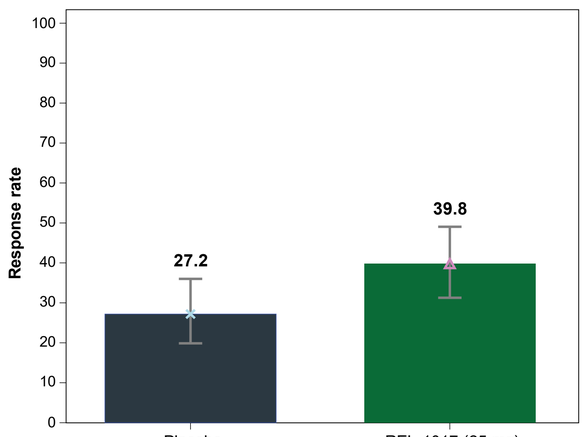

Figure 5. Response rate, ITT (N=227). The response rate at Day 28 was 39.8% for REL-1017 and 27.2% for placebo (*P*=0.0438; odds ratio=1.77).

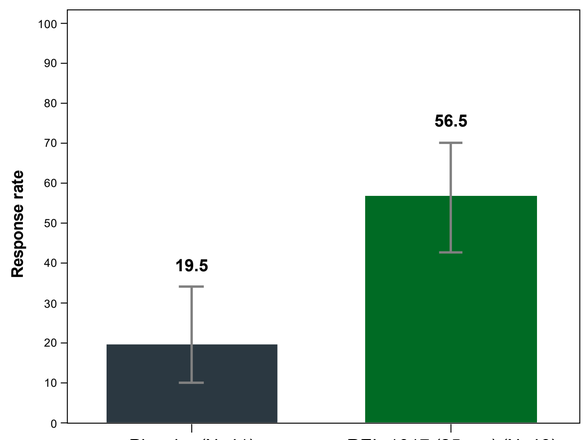

Figure 6. Response rate, ITT AT (N=87). The response rate at Day 28 was 56.5% for REL-1017 and 19.5% for placebo (*P*=0.0004; odds ratio=5.36).

Table 1. Baseline demographic characteristics, safety set (N=227).

Demographics		Safety set (N=227) N (%)
Years of age, mean (SD)		43.5 (14.6)
MADRS total score, mean (SD)		35 (4.8)
Body mass index (kg/m^2), mean (SD)		26.026 (3.035)
Sex		
	Male	58 (25.6)
	Female	169 (74.4)
Race		
	Asian	13 (5.7)
	Black/African American	30 (13.2)
	White	175 (77.1)
	Multiracial	6 (2.6)
	Other	3 (1.3)
Ethnicity		
	Hispanic or Latino	52 (22.9)
	Not Hispanic or Latino	164 (72.2)
	Not reported	9 (4)
	Unknown	2 (0.9)

Table 2. MADRS total score change from baseline at Day 28.

MADRS total score change from baseline at Day 28	PP (N=198)	ITT (N=227)	PP AT	ITT AT
Placebo mean (SD)	12.5 (9.9)	12.9 (10.4)	11.4 (9.0)	12.0 (9.5)
REL-1017 mean (SD)	15.6 (11.2)	15.1 (11.3)	17.5 (10.4)	17.3 (10.5)
REL-1017 vs placebo MD (SD)	3.1 (10.6)	2.3 (10.9)	6.1 (9.8)	5.4 (10.1)
P-value	0.0510	0.1537	0.0101	0.0232
Effect size	0.29	0.21	0.62	0.53

- In the PP population, the MD between REL-1017 and placebo in MADRS total score change from baseline at Day 28 was 3.1 (*P*=0.0510)
- In the PP AT group, there was a statistically significant MD of 6.1 (*P*=0.0101) for REL-1017 vs placebo in MADRS total score change from baseline at Day 28
- In the ITT population, there was a trend toward significance for the primary endpoint (*P*=0.1537) and a statistically significant difference in response rate (*P*=0.0438)
- In the ITT AT group, there was a statistically significant MD of 5.4 (*P*=0.0232) for REL-1017 vs placebo in MADRS total score change from baseline at Day 28 and a statistically significant difference in response rate (*P*=0.0004)

Table 3. Treatment-emergent adverse events (TEAEs), safety set (N=227).

Variable	Placebo (N=114)		REL-1017 25 mg (N=113)		All patients (N=227)	
	N	%	N	%	N	%
Patients with ≥1 TEAE*	61	53.5	55	48.7	116	51.1
Patients with ≥1 treatment-related TEAE	28	24.6	30	26.5	58	25.6
Patients with ≥1 serious treatment-related TEAE	0	0	0	0	0	0
Patients with TEAE leading to cessation or discontinuation of study drug	5	4.4	2	1.8	7	3.1
TEAEs occurring in 5% or more of patients per treatment arm						
Headache	9	7.9	13	11.5	22	9.7
COVID-19	10	8.8	6	5.3	16	7.0
Upper respiratory tract infection	6	5.3	8	7.1	14	6.2
Nausea	5	4.4	8	7.1	13	5.7
Diarrhea	7	6.1	5	4.4	12	5.3
Constipation	7	6.1	3	2.7	10	4.4
Dizziness	2	1.8	7	6.2	9	4.0

*TEAE is defined as an adverse event (AE) that starts or worsens at any time after initiation of study drug.

- Adverse events were primarily mild or moderate and transient
- There were no treatment-related serious adverse events

There were no indications of withdrawal or opioid abuse (data available at poster P.0166, "No Indication of Abuse Potential and Absence of Withdrawal From Esmethadone (REL-1017) in Patients With Major Depressive Disorder."

Twenty-nine patients in the ITT population were excluded from the PP population (17 placebo and 12 REL-1017).

- Eighteen (12 placebo and 6 REL-1017) did not complete treatment
- Ten (4 placebo and 6 REL-1017) experienced major protocol deviations
- One patient (placebo) did not complete treatment and experienced a major protocol deviation

CONCLUSIONS

- **In the prespecified PP population analysis, the efficacy of REL-1017 was considerably more favorable than that observed in the ITT analysis**
  - PP analyses may be better suited for evaluating drug efficacy compared to ITT in MDD trials assessing drugs like REL-1017 with a favorable side effect profile. While discrepancies in outcomes between ITT and PP populations are generally due to adherence [6], in our case, differences were not attributable to tolerability and safety adverse events impacting treatment compliance
  - "Professional patients" without MDD [7] may flatten the response to potentially effective antidepressant candidates, especially when testing drugs with no detectable psychoactive effects. We hypothesize that the ITT population may have included a higher proportion of "professional patients" and patients with transient reactive depression (perhaps related to COVID-19 pandemic stress) who were less motivated to complete treatment and assessments
- **The AT subgroup analyses from both the ITT and PP populations showed a significantly more robust efficacy of REL-1017 than those from the non-AT subgroups**
  - The AT subgroup's MDD history could have been better substantiated and established due to the careful assessment performed by the independent group of specialized MGH-CTNI clinicians and the use of their validated MGH ATRQ screening tool. These corroborative efforts may have helped screen out "professional patients" as well as those with transient reactive depression, resulting in a lower proportion of such patients
  - The favorable efficacy outcomes observed in the AT subgroups also raise the hypothesis that REL-1017 may have efficacy toward mitigating antidepressant tolerance, with a mechanism that is potentially mediated via NMDAR uncompetitive antagonism
- **Prespecified subgroup subanalyses of populations at higher risk for treatment failure may add insight to efficacy evaluations of novel antidepressant candidates**

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DISCLOSURES

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