MIN-117: A Randomized, Double-Blind, Parallel-Group, Placebo- and Active-Controlled Study to Evaluate Efficacy and Safety in Patients with Major Depressive Disorder

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Abstract

Background: MIN-117 is a benzofuran derivative characterized by its affinity for 5-HT_{1A}, 5-HTT, alpha (α)1 and 5-$HT_{2A,}$ 5-HT_{2C} receptors. MIN-117 is also active as a DA (DAT) and NE transporter. Because of its unique pharmacological profile it might address unmet needs in the depression treatment such as poor tolerability, late onset of efficacy and incomplete response.

Methods. This trial tested two doses of MIN-117, 0.5 mg and 2.5 mg, versus placebo with paroxetine as an active control to confirm assay sensitivity. Change from baseline on the MADRS was the main outcome measurement. As established prospectively this trial was designed for signal detection and effect size estimation. As such, it was not powered to demonstrate statistically significant differences between MIN-117 and placebo.

Results. A dose-dependent superiority of MIN-117 over placebo was demonstrated at the 0.5 mg daily dose with an effect size (ES) of 0.23 while the 2.5 mg dose had an ES of 0.33. Twenty four percent of the patients treated with MIN-117 2.5 mg achieved remission as prospectively defined. Both doses of MIN-117 demonstrated a favorable tolerability profile, and the incidence and types of AE did not differ between MIN-117 and placebo. Paroxetine also differentiated from placebo confirming assay sensitivity. Treatment with MIN-117 was not associated with cognitive impairment, sexual dysfunction, suicidal ideation or weight gain. MIN-117 preserved sleep continuity and architecture and therefore is not expected to have detrimental effects on rapid eye movement distribution and duration unlike most marketed antidepressants.

Conclusion. MIN-117 may address certain shortcomings of currently available antidepressants.

Study registration: EudraCT Number: 2015-000306-18

Background:

- MIN-117 is a benzofuran derivative characterized by its affinity for 5-HT_{1A}, 5-HTT, alpha (α)1 and 5-$HT_{2A,}$ 5-HT_{2C} receptors.
- MIN-117 is also active as a DAT and NE transporter.
- Rodent data indicate cognitive benefits after stress.
- The DAT activity might be the main driver of the beneficial effect of the drug on vigilance, attention and as a consequence, on cognition.
- In rodents MIN-117 appears superior to paroxetine in preserving sexual functioning.

Objectives:

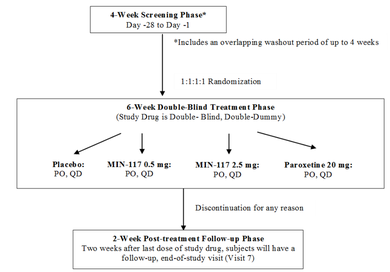
- To evaluate the efficacy of MIN-117 0.5 and 2.5 mg compared to placebo in reducing the symptoms of a major depressive episode as measured by the change from Baseline in the MADRS total score over 6 weeks of treatment.

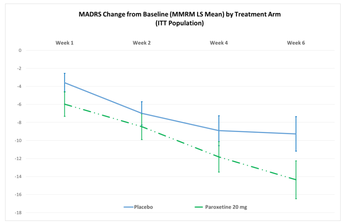
Methods:

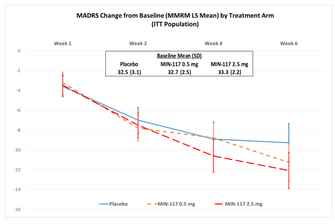
- Inclusion criteria: DSM-5 criteria for moderate or severe depression without psychotic features based on clinical assessment and on the MINI, v7.0, history of at least one previous episode of depression prior to the current episode; current major depressive episode of at least 8 weeks in duration; MADRS ≥ 30 at Screening (Visit 1) and Baseline (Visit 2a); score of ≥ 4 on the investigator-rated CGI-S at Screening (Visit 1) and Baseline (Visit 2a).
- Exclusion criteria: Other DSM-5 diagnoses (OCD, PTSD, anorexia, psychotic disorders, bipolar disorder, mental retardation, cluster B personality disorders, substance abuse, mood disorder with postpartum onset, somatoform disorders, chronic fatigue syndrome, or fibromyalgia); moderate or high risk of violence or suicide; treatment with ECT, TMS or VNS within past 6 months).
- The study was a four-arm, parallel-group, randomized double-blind, placebo- and positive-control trial which tested two daily administered doses of MIN-117: 0.5 mg and 2.5 mg. The study included 84 patients (21 per arm) with moderate to severe MDD in four European countries.

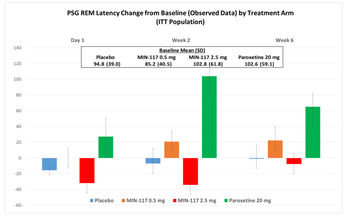
- Study design
  - Patients were randomized to placebo, oral MIN-117 0.5 mg/day, 2.5 mg/day or, paroxetine 20 mg in a 1:1:1:1 ratio.
  - Assessments for efficacy and safety were conducted at baseline before the first dose of medication and at weeks 1, 2, 4 and 6 or upon premature termination. A follow-up visit was performed at week 8.

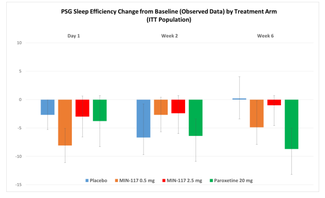
Figure 1: Study Design Diagram (Timelines not to scale)

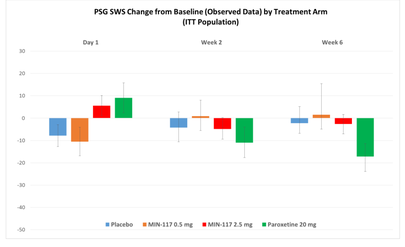












- Outcome measures
  - Primary outcome: Change from Baseline MADRS total score over 6 weeks of double blind treatment.
  - Secondary outcomes: CGI-S, CGI-I , HAM-A, Arizona Sexual Experiences Scale (A-SEX), Digit-Symbol Substitution Test (DSST), Towers of London Test, and Digit Span Backwards Task
  - Safety was evaluated by monitoring the frequency, severity and timing of adverse events, clinical laboratory test results, 12-lead EKG, vital signs measurements, body weight, S-STS and AIMS.

Results:

- A dose-dependent superiority of MIN-117 over placebo as measured by change on the MADRS was demonstrated starting at 2 weeks.
- MIN-117 at the 0.5 mg daily dose had an ES compared to placebo of 0.24 while the 2.5 mg dose had an ES of 0.34.
- Twenty four percent of the patients treated with MIN-117 2.5 mg achieved remission as prospectively defined (<12 Total MADRS score).
- Compared to placebo, the number of patients on the 2.5 mg dose who achieved remission had an odds ratio (OR) by Week 4 of 2.1 (0.5 for paroxetine), and by Week 6 of 3.1 (1.1 for paroxetine).
- The 2.5 mg dose was superior to paroxetine when evaluating the rate of response based on the definition of reduction in the MADRS score by ≥ 50%.
- As compared to placebo, the OR for the 2.5 mg and paroxetine were: Week 2 – 2.7 versus 1.2; Week 4 – 4.9 versus 3.0; Week 6 – 1.9 versus 1.6.
- MIN-117 preserved sleep continuity and architecture.
- Paroxetine also differentiated from placebo, confirming assay sensitivity.

Safety:

- Both doses of MIN-117 demonstrated a favorable tolerability profile, and the incidence and types of side effects did not differ significantly between MIN-117 and placebo.
- Treatment with MIN-117 was not associated with worsening of cognitive impairment or sexual dysfunction. No suicidal ideation or weight gain were observed.

Discussion:

- MIN-117 is a well tolerated antidepressant with a novel mechanism of action that might address certain shortcomings of currently available antidepressants. Appropriately powered Phase 3 trials should be designed to confirm these results.

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