Effect of MIN-101 on Cognitive Functioning in Stable Schizophrenia Patients with Negative Symptoms: A 12-Week Randomized, Double Blind, Placebo-Controlled Trial

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ABSTRACT

Background

- MIN-101 is a novel cyclic amido derivative, with high affinities for sigma$_2$ and 5-HT$_{2A}$ receptors. This a-priori designed analysis investigated the effect of MIN-101 on cognitive functioning.

Objectives:

- Compare the efficacy of MIN-101 to placebo on negative symptoms as a primary objective, and on impaired cognitive functioning as a secondary objective, in stable schizophrenia patients with negative symptoms

Methods

- Inclusion criteria: DSM-5 schizophrenia confirmed by MINI, symptomatically stable, manifesting negative symptoms over the 3 months prior, baseline score ≥ 20 on the 7 item negative symptoms scale of the PANSS and scores < 4 on the PANSS: excitement, hyperactivity, hostility, suspiciousness, uncooperativeness, and poor impulse control.
- Cognitive function was evaluated using the Brief Assessment of Cognition in Schizophrenia (BACS) just prior to drug administration as well as 4 weeks and 12 weeks after treatment initiation. BACS subscale raw scores were converted to age and gender corrected z scores and composite z scores. The Mixed-Effect Model Repeated Measure (MMRM) with Last Observation Carried Forward (LOCF) was used to compare the BACS subscales and composite scores; violation of normality assumption (Shapiro-Wilk W p-value ≤ 0.01) and examination of Q-Q plots were assessed across treatment groups.

Results

The three treatment groups were balanced on all demographic and illness-related baseline characteristics. At baseline, the age and gender-adjusted BACS composite score (z) were -2.103, -2.077 and -1.967 for the placebo, MIN-101 32 mg, and MIN-101 64 mg, respectively. Following LOCF, the MIN-101 32 mg was superior to placebo after 12 weeks of treatment on the composite z score ($p \leq 0.05$; Effect size: 0.439). The 64 mg dose was did not have a statistically significant effect compared to placebo.

Conclusions

Overall, MIN-101 at both doses showed quantitative superiority over placebo on most subscales and composite scores. The 32 mg/day dose was statistically superior to placebo on the composite score.

Background:

- MIN-101 is a novel cyclic amido derivative, which has high affinities for sigma$_2$ and 5-HT$_{2A}$ receptors. Although MIN-101 has no affinities for DA receptors it is very probable that sigma$_2$ receptors are implicated in the modulation of DA and glutamatergic pathways

METHODS

Subjects

244 subjects, 18 to 60 years of age, who met the diagnostic criteria for schizophrenia as defined in the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-V), as established by a full psychiatric interview in conjunction with the Mini International Neuropsychiatric Interview (MINI).

Study Design

- Patients were withdrawn from depot antipsychotics for ≥ 1 month and from all psychotropic drugs for ≥ 3 days prior to randomization.
- Patients were randomized to oral MIN-101 32 mg/day, 64 mg/day or, placebo in a 1:1:1 ratio.
- Patients were hospitalized for at least 3 days prior to randomization. Two days after randomization patients could be discharged or continue as inpatients at discretion of investigator.
- No psychotropic medications were allowed during the 12-week trial duration except for rescue medications given for insomnia or agitation (oral lorazepam, zolpidem, or injectable sodium amytal).

Assessments

Cognitive function was evaluated using the Brief Assessment of Cognition in Schizophrenia (BACS) just prior to drug administration as well as 4 weeks and 12 weeks after treatment initiation.

Statistical Analysis

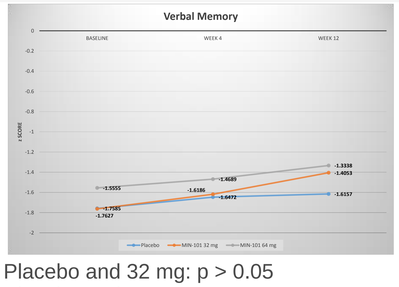
- BACS subscale raw scores were converted to age and gender corrected z scores and composite z scores.
- The Mixed-Effect Model Repeated Measure (MMRM) with Last Observation Carried Forward (LOCF) was used to compare the treatment effect of MIN-101 compared to placebo on the BACS subscales and composite scores.

RESULTS

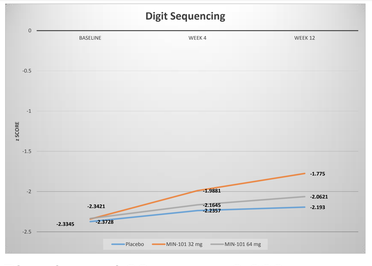
Treatment Group	Composite z score Baseline			Composite z Score Week 4			Composite z Score Week 12		
	Mean	Std. Deviation	N	Mean	Std. Deviation	N	Mean	Std. Deviation	N
Placebo	-2.103	1.18	53	-1.917	1.21	53	-1.879	1.17	53
MIN-101 32 mg	-2.077	1.22	48	-1.755	1.21	48	-1.567	1.23	48
MIN-101 64 mg	-1.967	1.14	52	-1.752	1.12	52	-1.642	1.16	52
Total	-2.048	1.17	153	-1.810	1.17	153	-1.701	1.18	153

Cognitive Composite		Mean Difference	Std. Error	Sig.
Placebo	MIN-101 32 mg	-.286*	.102	.017
	MIN-101 64 mg	-.101	.100	.938
MIN-101 32 mg	MIN-101 64 mg	.185	.103	.221

There was a statistically significant difference across treatment groups ($F(2,152) = 4.004$, $p = 0.020$) on the BACS composite score with the 32 mg group showing significant differences from placebo.

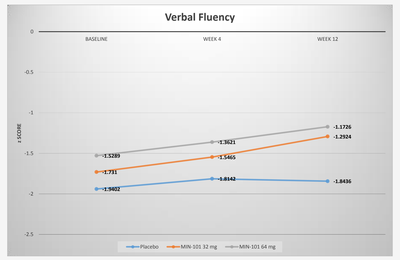


Placebo and 32 mg: p > 0.05
Placebo and 64 mg: p > 0.05

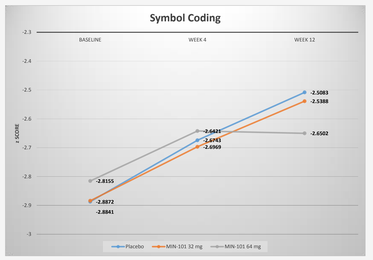


Placebo and 32 mg: p = 0.020
Placebo and 64 mg: p > 0.05

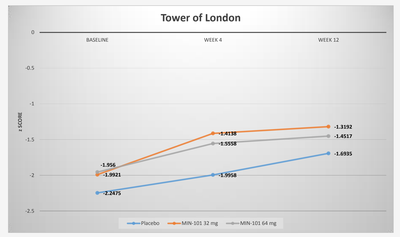
RESULTS



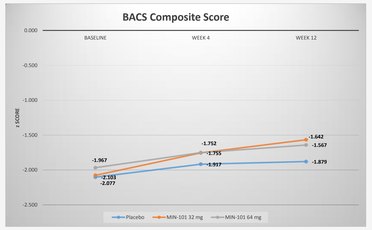
Placebo and 32 mg: p = 0.015
Placebo and 64 mg: p = 0.011



Placebo and 32 mg: p > 0.05
Placebo and 64 mg: p > 0.05



Placebo and 32 mg: p = 0.010
Placebo and 64 mg: p = 0.013



Placebo and 32 mg: p = 0.017
Placebo and 64 mg: p > 0.05

CONCLUSIONS

Overall, MIN-101 at both doses showed quantitative superiority over placebo on most subscales and composite scores. The 32 mg/day dose was statistically superior to placebo on the composite score. It is not clear why the improvement in cognitive functioning as measured by the BACS was larger with the 32 mg/day dose as compared to the 64 mg/day dose. These findings will be investigated in further studies.

DISCLOSURES AND CONTACT INFORMATION

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