A NEW DRUG IN DEVELOPMENT FOR NEGATIVE SYMPTOMS

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Is an effective, well-tolerated treatment for the negative symptoms of schizophrenia on the horizon?
• Negative symptoms in schizophrenia, including apathy, anhedonia, blunted affect, poverty of speech, and reduced social drive, are common and persistent despite currently available treatments
• The expert consensus Patient Outcomes Research Team schizophrenia guidelines state, “no pharmacologic treatment for negative symptoms has proved to have sufficient evidence to support a treatment recommendation”[1]
• Well-tolerated medications with efficacy for negative and cognitive symptoms of schizophrenia represent a huge area of unmet need
MIN-101 has equipotent affinities for sigma-2 and serotonin 5-HT2A receptors, but no direct dopamine affinities.

MIN-101 also has affinity for $\alpha_1$ receptors, but not cholinergic or histaminergic receptors.

In rodent models, MIN-101 has been associated with improvements in social interaction and spontaneous alternation behavior, and reduced hyperlocomotion, and does not have sedative effects.
MIN-101 in Schizophrenia

In a 12-week phase 2a randomized controlled trial (RCT) in patients with acute schizophrenia, MIN-101 was associated with significant improvement in negative symptoms versus placebo[2].

Study Methods

• The authors enrolled 244 patients (age 18 to 60) with a DSM-5 schizophrenia diagnosis at 36 sites across 6 European countries between May and December 2015
• Inclusion criteria were: clinically stable according to their psychiatrist; negative symptoms for at least 3 months and a baseline Positive and Negative Syndrome Scale (PANSS) negative subscale score of ≥20; and scores <4 for PANSS excitement, hyperactivity, hostility, suspiciousness, uncooperativeness, and poor impulse control items
• Exclusion criteria were: personal or family history of prolonged QT interval, CYP2D6 poor metabolizers, significant suicide risk, unstable medical disorder, or recent substance use
Study Methods-2

• Participants were hospitalized and withdrawn from all psychotropic medications for at least 5 days (at least 1 month for long-acting injectable antipsychotics)
• Participants were randomized to placebo or oral MIN-101 at 32 or 64 mg/d in a 1:1:1 ratio for 12 weeks. Assessments were completed at baseline and weeks 2, 4, 8, and 12
• No other psychotropic medications were allowed except for rescue medications for insomnia or agitation, or anticholinergics for treatment-emergent extrapyramidal symptoms
• The primary outcome measure was the PANSS negative factor score (pentagonal structure model)
• Secondary outcomes included PANSS total and subscale scores, Brief Negative Symptom Scale scores, Clinical Global Impressions Scale (CGI) scores, cognition (Brief Assessment of Cognition in Schizophrenia [BACS]), and depression (Calgary Depression Scale for Schizophrenia [CDSS])
• Data for the primary endpoint (change from baseline to week 12 in PANSS negative factor score) were analyzed with mixed-effects models, using all observed data without imputation of missing values
• 244 patients (100% Caucasian; 56% male; median age, 41; mean BMI, 26) were randomized and received at least one dose of study medication
• Subjects had a mean baseline PANSS total score of 80
• At week 12, there was a significant reduction in the PANSS negative factor score in both the 32 mg/d and 64 mg/d groups versus placebo (effect sizes of 0.45 and 0.57, respectively)
Significant improvements in negative symptoms were seen in both MIN-101 groups at 8 weeks, with benefit maintained at week 12. Improvement in negative symptoms was not driven by improvements in mood. The MIN-101 64 mg/d group also had significant improvements in PANSS total, CGI, CDSS, and BACS token motor scores compared with placebo at study endpoint.
Study Results-3

- There was no change in body weight or routine laboratory values from baseline in any subject groups
- 57% of patients in the MIN-101 groups reported at least one treatment-emergent adverse event
- The most common adverse events were headache, anxiety, and insomnia
Discussion

• The authors concluded that MIN-101 demonstrated statistically significant efficacy in reducing negative symptoms and good tolerability in stable schizophrenia patients.

• The authors noted that at this early stage of development it is difficult to weigh the meaningfulness of study results.
