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ABSTRACT

NW-3509A Targets new Mechanisms, and represents a new Approach to the Treatment of Schizophrenia

Laura Faravelli [1], Marco Bortolato [2], Emma Forrest [1], Mark T. Leibowitz [3], Ravi Anand [4]

[1]Newron Pharmaceuticals SpA, Bresso (MI), Italy; [2]Dept. of Neuroscience, Univ. of Cagliari (CA), Italy; [3]CNS Network Inc., Long Beach, Ca. US; [4]APC, AG, St. Moritz, Switzerland

Background
Aberrant electrical connectivity in schizophrenia that leads to abnormal cortical neuronal activity and glutamate transmission is not affected by existing drugs that target dysregulation of mesolimbic and mesocortical dopamine systems. NW-3509A, a new putative antipsychotic potently and selectively blocks VGSCs in a voltage-and use-dependent manner, modulates sustained repetitive firing without inducing impairment of the normal neuronal excitability, and inhibits glutamate release. Its potential benefits were demonstrated in a battery of animal models predictive of efficacy in psychiatric diseases including models of schizophrenia, psychosis, mania, depression, compulsivity and aggressiveness, and cognition. NW-3509A was effective when administered alone and in combination with marketed antipsychotics demonstrating the potential to reduce the therapeutic dose of antipsychotics. New results from preclinical studies and information from ongoing Phase I clinical trial are presented below.

Methods
Mechanism of action studies
New functional studies have been performed to investigate NW-3509A's mechanism. The effects of NW-3509A on monoamine levels and glutamate release were evaluated after acute administration of doses (2.5-5 mg/kg) active in rodent models of schizophrenia and mania.
Behavioral Studies
New behavioural studies included: 1) a double blind placebo-controlled study to assess the effect of NW-3509A monotherapy in the pre-pulse inhibition (PPI) deficit model in the rat; 2) the evaluation of NW-3509A as an add-on to haloperidol in a model of spontaneous PPI deficit in C57BL/6J mice; 3) the evaluation of NW-3509A as an add-on to risperidone in the amphetamine/chlordiazepoxide (amph/CDZ)-induced hyperactivity model in mice (mania model).

Results
Acute treatment with preclinical active doses of NW-3509A did not alter monoamines or their metabolites levels, while *in vivo* microdialysis studies in rats demonstrated that NW-3509A normalizes veratridine-stimulated glutamate release in the hippocampus without affecting basal release.
New data with NW-3509A used as monotherapy under double blind conditions with three placebo controls in the rat model of PPI deficit induced by amphetamine or MK-801 indicated that NW-3509A at doses of 1.25 and 5 mg/kg was significantly superior while another VGSC blocker carbamazepine, was not. The combination of haloperidol and inactive doses of NW-3509A significantly increased PPI compared to haloperidol alone in a model of spontaneous PPI deficit in C57BL/6J mice. In the amph/CDZ-induced hyperactivity model, an inactive dose of NW-3509A

produced an anti-manic effect when administered together with inactive doses of risperidone. Extrapolated plasma concentrations at effective doses in schizophrenia models range from 10 to 20 ng/ml.

Discussion

These results further extend the previously demonstrated benefits of NW-3509A either alone or in combination with first or second generation antipsychotics in animal models of mania, schizophrenia, and impaired information processing, irrespective of whether the impairment was induced by amphetamine, MK-801, scopolamine, or sleep deprivation. NW-3509A will target the abnormal cortical neuronal activity and glutamate transmission in patients with schizophrenia, and as it will be administered in conjunction with 5HT2/D_2 blocking anti-psychotics and will thus modulate major neurotransmitter systems that have been associated with positive symptoms in schizophrenia, and mania. Plasma concentrations exceeding 20 ng/ml have been achieved in a US Phase I study and a Phase II preliminary efficacy and safety study in patients with schizophrenia is planned for later this year.

Authors declare no conflict of interest