Ad hoc announcement pursuant to Art. 53 LR

Newron reports compelling topline results from all patients in Study 014, its Phase II clinical trial evaluating evenamide as add-on therapy for treatment-resistant schizophrenia

Results from all 161 patients at the 6-week primary endpoint show a statistically significant improvement over baseline in all efficacy measures

Results consistent with interim data from first 100 patients at this timepoint

Detailed Study 014 results to be presented at the 36th ECNP Congress

Milan, Italy, March 20, 2023, 07:00 am CET – Newron Pharmaceuticals S.p.A. ("Newron") (SIX: NWRN, XETRA: NP5), a biopharmaceutical company focused on the development of novel therapies for patients with diseases of the central and peripheral nervous system (CNS), announces exciting topline results from Study 014, a phase II, international, randomized, open label, rater-blinded trial evaluating evenamide as an add-on to an antipsychotic (excluding clozapine) in patients with moderate to severe treatment-resistant schizophrenia (TRS) not responding to their current antipsychotic medication. While the primary objective of the study was safety and tolerability of the drug, efficacy over baseline was also assessed. Interim results from the first 100 patients at six weeks were previously reported in June 2022.

Notably, of the 161 patients who were randomized, 153 (95%) completed the six-week treatment period and 144 (94% of the completers) entered the extension study (Study 015). One patient discontinued treatment due to flu-like symptoms, and seven withdrew consent.

Overall, the results from the complete study population are fully consistent with the findings from the first 100 patients at this timepoint. The mean Positive and Negative Syndrome Scale (PANSS) total score, Clinical Global Impression of Severity (CGI-S) rating, and the Strauss-Carpenter Level of Functioning (LOF) total score significantly improved compared to baseline ($p<0.001$). The proportion of patients considered "clinically important responders" on the PANSS, the Clinical Global Impression of Change (CGI-C) and the CGI-S was in line with the proportion of the first 100 patients experiencing this level of benefit after six weeks. Mean improvement from baseline was also consistent for the Medication Satisfaction Questionnaire (MSQ) when compared to this measure for the first 100 patients.

The number of patients who experienced treatment-emergent adverse events (TEAEs) was low (26%) and none was rated severe; the most commonly reported TEAEs (≥3%) were dizziness, pyrexia, and CPK increase. No treatment-emergent or clinically important findings for weight gain, metabolic syndrome, sexual dysfunction, neurological findings (based on ESRS-A and neurological examination), standard laboratory tests or electrocardiograms (ECGs) were reported. This adverse event profile was also similar to that seen from the first 100 patients.

Ravi Anand, M.D., Newron's Chief Medical Officer, said: *"The final results of study 014 are exciting for various reasons. Firstly, the results indicate that the last 61 patients to be enrolled in the study share the same demographic and disease improvement characteristics as of the first 100 patients, after six weeks of treatment. Treatment with evenamide at all doses (7.5, 15 or 30 mg bid) was also as well tolerated in the final 61 patients as was shown in the initial cohort of 100 patients, thus confirming the reliability of the data collected in this study.*

The tolerability and safety of the doses of evenamide in the last 61 patients was also largely similar to that reported earlier in terms of high completion rate, low discontinuation due to adverse events and very low incidence of adverse events.

Most importantly, the pattern of benefit associated with evenamide in these 61 patients was similar to the efficacy noted in the first 100 patients, without any evidence of systematic differences between doses of evenamide. Additionally, the efficacy benefits of evenamide in the analysis of all 161 patients at six weeks appeared very similar to the findings from the first 100 patients.

We are hopeful that these encouraging results at six weeks from all 161 patients in study 014 will be replicated at six months and one-year timepoints in all patients in study 015. Confirmation of these results in the final analyses would offer new hope to patients with TRS and would further support our plans for the initiation of study 003, a Phase III study in patients with TRS, which we intend to begin later in 2023."

Detailed results from study 014 will be presented at the 36th European College of Neuropsychopharmacology (ECNP) Congress, taking place 7-10 October 2023 in Barcelona, Spain. In addition, Newron will be presenting the results of the previously announced six-month endpoint from the first 100 patients at the 31st European Congress of Psychiatry taking place 25-28 March 2023, in Paris, France, and the one-year data at the Congress of the Schizophrenia International Research Society taking place 11-15 May 2023, in Toronto, Canada.

Newron expects to initiate a potentially pivotal, multinational, randomized, placebo-controlled trial in patients with TRS (study 003) in 2023, as part of its ongoing Phase II/III development plan for evenamide. The first potentially pivotal study of this development program, study 008A, with evenamide as add-on therapy in patients with chronic schizophrenia experiencing inadequate response to their current antipsychotics (but not diagnosed as having TRS) is enrolling patients, and results are expected in 2023.

Newron continues its dialogue with industry partners around potential future collaboration opportunities for the development of evenamide.

About treatment-resistant schizophrenia (TRS)
A significant proportion of patients with schizophrenia show virtually no beneficial response to antipsychotics (APs) despite adequate treatment, leading to a diagnosis of treatment-resistant schizophrenia (TRS). TRS is defined as no, or inadequate, symptomatic relief despite treatment with therapeutic doses of two APs from two different chemical classes for an adequate period. About 15% of patients develop TRS from illness onset, and about one-third of patients overall.

Increasing evidence supports abnormalities in glutamate neurotransmission in TRS, not targeted by current APs, along with normal dopaminergic synthesis, explaining the lack of benefit of most typical and atypical APs.

About evenamide
Evenamide, an orally available new chemical entity, specifically blocks voltage-gated sodium channels (VGSCs) and is devoid of biological activity at >130 other CNS targets. It normalizes glutamate release induced by aberrant sodium channel activity (veratridine-stimulated), without affecting basal glutamate levels, due to inhibition of VGSCs. Combinations of ineffective doses of evenamide and other APs, including clozapine, were associated with benefit in animal models of psychosis, suggesting synergies in mechanisms that may provide benefit in patients who are poor responders to current APs, including clozapine.

About study 014/015
Study 014 was a six-week, randomized, rater-blinded study conducted at multiple sites in three countries (India, Italy and Sri Lanka). Study 014 has enrolled 161 patients with TRS on a stable, therapeutic dose of a single antipsychotic other than clozapine. The primary objective of the study was to evaluate the safety and tolerability of evenamide given orally at three fixed doses (7.5, 15 and 30 mg bid). The assessment of preliminary efficacy was based on changes from baseline in the Positive and Negative Syndrome Scale (PANSS). Changes from baseline in Clinical Global Impression of Change (CGI-C), Severity of Illness (CGI-S), and Strauss-Carpenter Level of

Functioning (LOF) scale, have been secondary objectives. Study 015 is the extension study to determine the long-term benefits of glutamate release inhibition.

Study 014 included data from all 161 patients (69% male, 98% Asian, mean age 37.8 years, mean BMI 25.3 kg/m2) randomized to treatment with 7.5 (n= 50), 15 (n= 60) and 30 mg (n= 51) bid for six weeks. Patients were enrolled in India (88%), Sri Lanka (10%), and Italy (2%), and oral risperidone (55%) and olanzapine (26%) were the most frequent background antipsychotics. Schizophrenia had been diagnosed on average 6.8 years before screening, the current episode had lasted an average of 7.9 months, and the mean baseline, PANSS total score was 79.5, with a mean CGI-S rating of 4.5 and LOF score of 17.6. No meaningful differences in demographic, baseline and disease characteristics were noted between the three treatment groups. One patient discontinued treatment due to flu-like symptoms, and seven withdrew consent.

Seventy-seven (77) of the first 100 patients completed the 1-year of treatment with evenamide, 16 discontinued the study early, two due to adverse events (one patient due to fever, vomiting, and nausea, the other due to somnolence, reduced concentration and increased sweating), the other 14 due to withdrawal of consent or lost to follow up.

About Newron Pharmaceuticals
Newron (SIX: NWRN, XETRA: NP5) is a biopharmaceutical company focused on the development of novel therapies for patients with diseases of the central and peripheral nervous system. The Company is headquartered in Bresso near Milan, Italy. Xadago®/safinamide has received marketing authorization for the treatment of Parkinson's disease in the European Union, Switzerland, the UK, the USA, Australia, Canada, Latin America, Israel, the United Arab Emirates, Japan and South Korea, and is commercialized by Newron's Partner Zambon. Supernus Pharmaceuticals holds the commercialization rights in the USA. Meiji Seika has the rights to develop and commercialize the compound in Japan and other key Asian territories. Newron is also developing evenamide as the potential first add-on therapy for the treatment of patients with symptoms of schizophrenia. For more information, please visit: www.newron.com

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