Ad hoc announcement pursuant to Art. 53 LR

Newron announces approval for pivotal Phase III ENIGMA-TRS program with evenamide as add-on therapy in patients with treatment-resistant schizophrenia (TRS)

ENIGMA-TRS 1 *is an international, one-year, double-blind, placebo-controlled Phase III study in at least 600 patients; enrollment to start imminently; 12-week study results expected in Q4 2026*

ENIGMA-TRS 2*, approved by the US Food and Drug Administration (FDA), is a US-based and international, 12-week, double-blind, placebo-controlled Phase III study in at least 400 patients; study expected to start within the next three months*

Evenamide has the potential to become the first add-on therapy for patients suffering from TRS and for poorly responding patients with schizophrenia

Unique glutamatergic modulation mechanism of action offers new therapeutic option for this patient population

Milan, Italy, and Morristown, NJ, USA, May 12, 2025, 07:00 am CEST – 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, today announced the approval for its pivotal ENIGMA-TRS Phase III development program evaluating evenamide as an add-on therapy to current antipsychotics, including clozapine, in patients with treatment-resistant schizophrenia (TRS).

The ENIGMA-TRS Phase III development program consists of two pivotal studies, ENIGMA-TRS 1 and ENIGMA-TRS 2. The two studies are expected to meet the ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) specified regulatory requirements for submission of the registration dossier for evenamide in major territories, including the US and Europe.

ENIGMA-TRS 1 is an international, 52-week, randomized, double-blind, placebo-controlled Phase III study evaluating the efficacy, tolerability, and safety of the 15mg BID and 30mg BID therapeutic doses of evenamide compared to placebo. Patients on second-generation anti-psychotics (SGAs), including clozapine, will meet Treatment Response and Resistance Psychosis (TRRIP) international consensus criteria for TRS.

ENIGMA-TRS 1 will enroll at least 600 patients at study centers in Europe, Asia, Latin America and Canada. Patients will undergo a 42-day screening period, during which their TRS diagnosis, antipsychotic plasma levels (background medication), and conformance to protocol selection criteria will be evaluated by an Independent Eligibility Assessment Committee (IEAC) of three leading international schizophrenia experts.

The primary assessment of efficacy and safety will be performed 12 weeks after randomization to treatment. The study will continue double-blind and placebo-controlled until the 52-week (i.e. one year) time point. Enrolment to the study will start imminently. The 12-week results from the study are expected in Q4 2026.

ENIGMA-TRS 2, approved by the US Food and Drug Administration (FDA), will be performed at centers in the US and selected additional countries and will include at least 400 patients in a 12-week, randomized, double-blind, placebo-controlled Phase III study, designed to evaluate the efficacy, tolerability, and safety of the 15mg BID dose of evenamide. Patients will meet selection criteria and be reviewed by the above-mentioned IEAC. The analysis for determination of efficacy and safety will be performed after patients complete 12 weeks of participation in the trial. US investigational centers are expected to initiate the study within the next three months.

Stephen Marder, MD, Distinguished Professor of Psychiatry, Semel Institute of Neuroscience & Human Behavior, and Director, Section on Psychosis, UCLA Neuropsychiatric Institute, commented: *"The imminent initiation of ENIGMA-TRS 1 study of evenamide is a significant milestone in the search for new medications to treat this devastating condition. Evenamide's modulation of glutamate, good tolerability, and efficacy in studies performed to date, both in patients who are poor responders or treatment resistant to SGAs, suggests its therapeutic potential in patients with TRS. The field eagerly looks forward for results from this landmark trial."*

Jean-Pierre Lindenmayer, MD, Director of Research, Psychopharmacology Research Unit - Nathan Kline Institute for Psychiatric Research at Manhattan Psychiatric Center, added: *"Evenamide's selectivity for sodium channels and consequent modulation of glutamate, the demonstration of its efficacy in multiple animal models of psychosis as well as the MAM model of neurodevelopmental abnormalities, suggests promising results in patients with TRS. Completed studies in inadequate responders to SGAs and the results of a one-year study in patients with TRS predict therapeutic benefit of evenamide in TRS patients. Evenamide has the potential to fill a wide gap in our treatment for patients with incomplete response to SGAs, including clozapine. I look forward to participating to the ENIGMA-TRS 2 trial as a study center."*

Ravi Anand, MD, Chief Medical Officer of Newron, stated: *"Newron greatly appreciates the regulatory approval of the ENIGMA-TRS trials. The positive results of evenamide observed in clinical studies and demonstrated in disease models have led to high enthusiasm in investigators to participate in this landmark program."*

The Phase III ENIGMA-TRS clinical trials are part of Newron's development program for evenamide, targeting patients with schizophrenia experiencing worsening of psychosis on therapeutic doses of current antipsychotics, as well as treatment-resistant patients, which together account for the vast majority of patients suffering from schizophrenia.

Results from previous Phase II (study 014/015) and Phase III (study 008A) studies have demonstrated evenamide's significant and increasing efficacy as an add-on therapy on multiple measures of psychopathology in patients with TRS and inadequate responders, respectively. These results also confirmed a favorable safety and tolerability profile, adding to the growing evidence that evenamide's glutamatergic inhibition mechanism of action offers an innovative therapeutic option to schizophrenia patients who are not benefiting from current antipsychotic treatments.

Newron has entered into licensing agreements with EA Pharma, a subsidiary of Eisai, in Japan and other designated territories, and with Myung In Pharm in South Korea, to develop, manufacture and commercialize evenamide in the respective territories. Under the terms of the agreements, Newron will receive up to a maximum total of EUR 117 million, including an upfront payment of EUR 44 million, financial contributions to the Phase III ENIGMA-TRS program, milestone payments, and tiered royalties up to a double-digit percentage of net sales for evenamide, from EA Pharma; Myung In Pharm will contribute 10% of the total patient population to be enrolled into Newron's upcoming Phase III ENIGMA-TRS trial and cover the costs related to this population.

Newron is actively exploring additional partnerships for the global development and commercialization of evenamide.

About schizophrenia

Approximately 25 million people worldwide are affected by schizophrenia. Despite more than 60 different types of atypical and typical antipsychotics used to treat schizophrenia globally, a considerable number of patients remain severely ill or resistant to treatment. Overall, 30-50% of patients do not respond to the available medications and are defined as treatment resistant. In addition to the patients with treatment-resistant schizophrenia (TRS), another 20-30% are described as "poor responders to anti-psychotic medication", even if not meeting the criteria for TRS. New findings indicate that patients with TRS have abnormalities in the glutamatergic system, but not in dopaminergic transmission, so there is a significant unmet medical need for treatments with a glutamatergic mechanism of action, efficacious both in TRS patients and in those who are poor responders to the current treatments.

About evenamide

Evenamide is the first new chemical entity that has demonstrated significant benefits in this difficult-to-treat patient population, as seen in the potentially pivotal Phase III study 008A trial, as an add-on treatment to second generation anti-psychotics including clozapine, in 291 poorly responding patients with chronic schizophrenia. The primary endpoint, the Positive and Negative Syndrome Scale (PANSS)[1], and the key secondary endpoint, the Clinical Global Impressions Scale – Severity (CGI-S), were met and showed statistical significance compared to placebo. Importantly, evenamide treatment was associated with statistically significant increases in the proportion of patients who experienced "clinically meaningful benefit" on the outcome variables. Evenamide was extremely well tolerated, without any of the usual side effects of available anti-psychotics.

About Newron Pharmaceuticals

Newron (SIX: NWRN, XETRA: NP5) is a biopharmaceutical company focused on developing novel therapies for patients with diseases of the central and peripheral nervous system.

Headquartered in Bresso, near Milan, Italy, Newron is advancing its lead compound, evenamide, a first-in-class glutamate modulator, which has the potential to be the first add-on therapy for treatment-resistant schizophrenia (TRS) and for poorly responding patients with schizophrenia. Evenamide is currently in Phase III development and clinical trial results to date demonstrate the benefits of this drug candidate in the TRS patient population, with significant improvements across key efficacy measures increasing over time, as well as a favourable safety profile, which is uncommon for available antipsychotic medications.

Newron has signed development and commercialization agreements for evenamide with EA Pharma (a subsidiary of Eisai) for Japan and other Asian territories, as well as Myung In Pharm for South Korea.

Newron has a proven track record in bringing CNS therapies to market. Its Parkinson's disease treatment, Xadago® (safinamide), is approved in over 20 markets, including the USA, UK, EU, Switzerland, and Japan, and commercialized in partnerships with Zambon and Meiji Seika.

For more information, please visit: www.newron.com

1 Positive and Negative Syndrome Scale (PANSS) is widely used in clinical trials of schizophrenia and is considered the "gold standard" for assessment of antipsychotic treatment efficacy (Innvo Clin Neurosci, 2017: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5788255/)

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