**Ad hoc announcement pursuant to Art. 53 LR**

# Newron announces the US initiation of its ENIGMA-TRS 2 Phase III global clinical study with evenamide as an add-on therapy for patients with treatment-resistant schizophrenia (TRS)

*ENIGMA-TRS 2 is a global, randomized, double-blind, placebo-controlled 12-week Phase III clinical study designed to enroll at least 400 patients; topline results are expected by Q4 2026*

*Evenamide is a first-in-class glutamate modulator with a novel mechanism of action for patients who do not respond adequately or are resistant to existing antipsychotic therapies*

*Newron's ENIGMA-TRS program (ENIGMA-TRS 1, started in August 2025, and ENIGMA TRS 2) aims to establish evenamide as the first approved add-on therapy for TRS, providing a new treatment option for a patient population with high morbidity and mortality*

**Morristown, NJ, USA, and Milan, Italy, December 8, 2025, 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, today announced the initiation of its ENIGMA-TRS 2 Phase III clinical study in the US, following approvals from the US Food and Drug Administration (FDA) and the Institutional Review Board (IRB). The first site to initiate the study will be the Semel Translational Research Center for Neuropsychiatry (TRCN), University of California, Los Angeles (UCLA). The remaining US sites participating in ENIGMA-TRS 2 are expected to initiate the study shortly. Regulatory submissions are currently being made in the other countries that are expected to participate in this trial in the coming months.

"*This study addresses a significant unmet medical need in patients with treatment-resistant schizophrenia who are not responding to their current second-generation antipsychotic medication. Previous studies in patients who are inadequate responders and with treatment-resistant schizophrenia have demonstrated clinically meaningful benefits of evenamide with no evidence of intolerance*", said Prof. Stephen Marder, Director of the Section on Psychosis at the UCLA Semel Institute for Neuroscience and Human Behavior, principal investigator for the study.

**ENIGMA-TRS 2: A Global Phase III Study Bringing New Hope to Patients with TRS in the US and other countries**

ENIGMA-TRS 2 is a Phase III, global, 12-week, randomized, double-blind, placebo-controlled trial evaluating the efficacy, safety, and tolerability of evenamide 15 mg twice daily as an add-on therapy to current antipsychotics, including clozapine, compared to placebo, in patients suffering from TRS. Eligible patients must meet the Treatment Response and Resistance In Psychosis (TRRIP) international consensus criteria for TRS.

The ENIGMA-TRS 2 study design has been approved by the US FDA and the study will enroll at least 400 patients across the US, Europe, Asia, and Latin America. Prior to randomization, patients undergo a 42-day screening period, during which their TRS diagnosis, plasma levels of their background antipsychotic medication, and adherence to protocol-defined eligibility criteria will be evaluated by an Independent Eligibility Assessment Committee (IEAC) comprising leading international experts in the field of schizophrenia research.

The primary assessment of efficacy and safety will be performed 12 weeks after randomization to treatment; topline results are expected in Q4 2026.

Earlier clinical trials (Phase II studies 014/015 and Phase III study 008A) demonstrated that evenamide, when added to standard antipsychotic therapy, was well tolerated and safe. Importantly, evenamide may lead to clinically meaningful improvements for people who fail to respond or become resistant to other antipsychotic treatments. Patients in previous trials experienced increasing and sustained symptom improvement, suggesting that evenamide's unique mechanism of action of modulating excessive glutamatergic activity in the brain could represent a crucial novel approach in the treatment of schizophrenia.

The ENIGMA-TRS pivotal Phase III program consists of ENIGMA-TRS 1 and ENIGMA-TRS 2. ENIGMA-TRS 1, initiated in August 2025 and currently enrolling patients on all three target continents, is an international, one-year, double-blind, placebo-controlled study in at least 600 patients to evaluate the efficacy, tolerability, and safety of two daily doses: 15mg and 30mg. Both studies represent a key component of Newron's global development strategy for evenamide, targeting patients with schizophrenia, experiencing treatment resistance to current antipsychotics. According to current literature, up to 50% of patients suffering from schizophrenia are classified as treatment-resistant, underscoring the urgent need for new, effective therapeutic options.

Prof. Marder's comments reflect his professional assessment as a study investigator and do not constitute an endorsement by the University of California, Los Angeles.

***About treatment-resistant schizophrenia (TRS)***

A significant proportion of patients with schizophrenia show virtually little to no beneficial response to currently available antipsychotic (AP) treatments, leading to a diagnosis of treatment-resistant schizophrenia (TRS). TRS is defined as no or inadequate symptom relief despite treatment with therapeutic doses of two APs from two different chemical classes for an adequate period. It is estimated that approximately 15% of patients develop TRS from the onset of illness, and about one-third to 50% of patients with schizophrenia overall. Emerging scientific evidence supports abnormalities in glutamate neurotransmission in TRS, not targeted by current APs, along with normal dopaminergic synthesis, to explain the lack of clinical benefit of most typical and atypical antipsychotics, which act primarily on dopamine receptors. These insights underline the need for novel therapeutic approaches that target the underlying glutamatergic dysfunction in schizophrenia, offering hope for patients who currently have limited or no effective treatment options.

***About evenamide***

Evenamide is a novel, orally available new chemical entity with a unique mechanism of action distinct from all currently marketed antipsychotics. It acts by selectively blocking voltage-gated sodium channels (VGSCs) and exhibits no biological activity at more than 130 other central nervous system (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 subtherapeutic doses of evenamide and other APs, including clozapine, were associated with benefit in animal models of psychosis, suggesting synergies in mechanisms that may provide meaningful benefits for patients who do not adequately respond to current APs, including those on clozapine. Importantly, the benefits seemed to persist for a substantial time after evenamide had been degraded, explaining the long-term effects seen in clinical studies. Through its novel glutamatergic modulation, evenamide represents a first-in-class approach aimed at addressing the unmet needs of patients with schizophrenia who are resistant to existing treatments.

***About Newron Pharmaceuticals***

Newron (SIX: NWRN, XETRA: NP5) is a biopharmaceutical company focused on the development of innovative therapies for patients with diseases of the central and peripheral nervous system. Headquartered in Bresso near Milan, Italy, the Company has a strong track record of advancing neuroscience-based treatments from discovery to market. Newron's lead compound, evenamide, is a first-in-class glutamate modulator and 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 developed in the global pivotal ENIGMA-TRS Phase III development program. Clinical trial results to date demonstrate the benefits of this drug candidate in the TRS as well as poorly responding patient population, with significant improvements across key efficacy measures increasing over time, as well as a favorable 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's first marketed product, 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. The product is commercialized by Newron's partner Zambon, with Supernus Pharmaceuticals holding marketing rights in the U.S., and Meiji Seika responsible for development and commercialization in Japan and other key Asian territories. For more information, please visit: www.newron.com

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**Important Notices**

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