Newron Notes Publication Highlighting Clinically Meaningful Benefits of Evenamide as an Adjunctive Treatment in Schizophrenia

Publication presents clinical findings highlighting evenamide's glutamatergic modulation as a therapeutic strategy for patients with inadequate response or treatment-resistant schizophrenia (TRS)

By targeting the hippocampus region of the brain, evenamide addresses schizophrenia at the source of dysfunction

Milan, Italy, and Morristown, NJ, USA, February 3, 2026 – Newron Pharmaceuticals S.p.A. ("Newron") (SIX: NWRN, XETRA: NP5), a biopharmaceutical company focused on developing novel therapies for patients with diseases of the central and peripheral nervous system, today announced the publication of peer-reviewed data in *Therapeutic Advances in Psychopharmacology,* co-authored by Newron's Chief Medical Officer, Ravi Anand, MD, and colleagues[1]. The publication presents clinical findings showing that evenamide, a novel glutamate modulator, is associated with clinically meaningful and sustained benefits when added to first- or second-generation antipsychotics in patients with schizophrenia who have an inadequate response to existing treatments, including those with TRS.

The publication synthesizes results from multiple randomized clinical trials and provides a scientific mechanistic rationale for the use of evenamide as a unique approach that targets disease mechanisms not addressed by existing antipsychotics. Drawing on data and analyses from randomized clinical studies, the publication highlights how modulation of aberrant glutamatergic signaling may deliver clinically meaningful benefits for patients with TRS and for those who continue to struggle despite standard antipsychotic treatment.

"This publication captures more than a decade of scientific and clinical work addressing one of psychiatry's most difficult challenges," **said Ravi Anand, MD, Chief Medical Officer at Newron Pharmaceuticals.** *"The analyses highlight not only symptom improvement but also real-world functional gains that matter to people living with schizophrenia, particularly those who have exhausted available options."*

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A Distinct Mechanism Targeting the Site of Dysfunction

Unlike currently marketed antipsychotics that act primarily by blocking dopamine receptors in the basal ganglia, evenamide's primary site of action is the hippocampus, that controls hyperdopaminergic firing in the basal ganglia (a brain region intimately involved in the causation of the core symptoms of schizophrenia). By reducing excessive glutamate activity in the hippocampus, evenamide indirectly rebalances dopamine signaling while preserving normal neuronal function. The hippocampal site of action of evenamide may explain why evenamide has demonstrated improvements not only in positive symptoms but also in negative symptoms, social functioning, and life engagement – domains that together with cognition are controlled by the various nuclei in the hippocampus and remain largely unaddressed by existing therapies. Taken together, the findings support evenamide as a potential first-in-class adjunctive therapy capable of redefining expectations for patients with TRS.

Across clinical studies reported to date, evenamide has maintained a favorable safety and tolerability profile, being well-tolerated, with low rates of treatment discontinuation and no consistent pattern of serious safety concerns.

"Evenamide represents a fundamentally different treatment approach," said Anand. *"By targeting the hippocampus – the source of the deficit rather than its downstream effects – we believe evenamide has the potential to shift the treatment paradigm, particularly for patients with TRS who urgently need new options."*

Clinically Meaningful and Durable Benefits

The publication reports analyses from two key clinical programs. In a one-year study of patients with treatment-resistant schizophrenia, more than half of those patients treated with evenamide improved to such an extent that they no longer met the severity criteria for TRS after long-term adjunctive treatment. Approximately one-quarter achieved remission, based on the most stringent criteria for remission.

In a separate randomized, double-blind, placebo-controlled trial among patients with inadequate response to antipsychotics, evenamide showed statistically significant improvements over standard of care, regardless of the number of prior failed treatments. Importantly, benefits were observed not only in core symptoms but also in measures of social functioning and life engagement, domains often poorly addressed by existing therapies.

"These results are notable because they go beyond symptom reduction," continued Anand. *"With evenamide, we are seeing improvements that translate into patients' daily lives, including their ability to function, engage socially, and potentially move closer to remissio*n. *That is a meaningful outcome for patients, families, and clinicians."*

Newron is advancing evenamide through ENIGMA-TRS, an international Phase III clinical program for patients with documented TRS. If successful, these studies could support the use of evenamide as a first-in-class adjunctive therapy, addressing a long-standing gap in the treatment landscape.

About ENIGMA-TRS

The ENIGMA-TRS pivotal Phase III program consists of ENIGMA-TRS 1 and ENIGMA-TRS 2. ENIGMA-TRS 1, initiated in August 2025, is an international, one-year, double-blind, placebo-controlled study in at least 600 patients to evaluate the efficacy, tolerability, and safety of evenamide 15 mg and 30 mg twice daily as an add-on therapy to current antipsychotics, including clozapine, compared to placebo. ENIGMA-TRS 2, initiated in December 2025, is a Phase III, international, 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. ENIGMA-TRS 2 will enroll at least 400 patients.

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 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 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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