Ad hoc announcement pursuant to Art. 53 LR

Newron reports exceptional one-year results of study 014/15 with evenamide in treatment-resistant schizophrenia (TRS)

Treatment with evenamide demonstrated significant, clinically important, progressive, sustained and long-lasting improvement on PANSS total, CGI-S and Level of Functioning (LOF)

More than 70% of patients experienced clinically important reduction in disease severity

25% of all patients achieved “remission”

No patient relapsed during the one-year treatment period

Never before seen results for evenamide, a glutamate modulator, suggest transformative management and societal outlook for patients with TRS

Company prepares for a potentially pivotal, Phase III, one-year, randomized, double-blind, placebo-controlled TRS trial

Milan, Italy, January 4, 2024, 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), today reported positive final, one-year results from its open label study 014/015, evaluating its investigational drug evenamide as an add-on to antipsychotics for the management of treatment-resistant schizophrenia (TRS). The data demonstrated that treatment with evenamide was associated with sustained clinically significant benefit that increased throughout the one-year course of treatment.

Final results at one-year indicate that the addition of evenamide to antipsychotics was well tolerated, with a low incidence of treatment-emergent adverse dropouts, and without any pattern of motor or CNS symptoms, weight gain, sexual dysfunction or laboratory/electrocardiogram (EKG) abnormalities. Of the 161 TRS patients randomized in the study, 75% completed one-year of treatment: the causes of attrition were withdrawal of consent (14.3%), not rolling over into extension study (5.6%), lost to follow up (3.1%), and adverse dropouts (ADOs) (1.9%).

Study 014/015 key findings and conclusions at one-year (full study population):

- Efficacy results based on change from baseline in the Positive and Negative Syndrome Scale (PANSS), the Clinical Global Impression of Severity (CGI-S), and the Strauss Carpenter Level of Functioning (LOF) showed a statistically significant improvement at one year (p-value < 0.001: paired t-test, OC/LOCF). All efficacy scales showed gradual and sustained improvement.
- In contrast to common clinical experience, no patient "relapsed" during the one-year treatment period.
- More than 70% of the patients experienced clinically important reduction in disease severity.
- Approximately 90% of the patients who had responded to the treatment by a clinically important reduction (≥ 20% from baseline) on PANSS total score at six months (~45%) maintained their response at one-year.
- Review of the efficacy data indicated that treatment with evenamide resulted in approximately 50% of patients at one-year no longer meeting any of the protocol severity criteria used to diagnose treatment resistance.
- 25% of all patients achieved "remission" (see "About remission"), never described before in TRS patients.

The durability and longevity of these clinical benefits is unprecedented and strongly raises the expectation for an improved evidenced-based treatment strategy for TRS patients, i.e. the addition of a glutamate modulator to background antipsychotics. Furthermore, the findings support the initiation of a potentially pivotal, Phase III, randomized, double-blind, placebo-controlled study of two doses of evenamide (15 and 30 mg bid) as an add-on treatment in patients with TRS.

Ravi Anand, Newron's Chief Medical Officer, said: *"Treatment with evenamide as an add-on to antipsychotics in TRS patients has produced benefits that have never been reported before. Despite these patients being on therapeutic doses of antipsychotics, evenamide treatment was associated with clinically important improvement (≥20%) on PANSS in approximately 40% of patients, functioning (LOF) in over 60% of patients, and reduction in the severity of disease (CGI-S) in over 70% of patients.*

Regardless of the criteria applied for remission in patients with chronic schizophrenia, approximately 25% of these treatment-resistant patients were considered in remission using the most quoted criteria[1]. Although these data are derived from an open-label study, the increasing benefit over time from six-weeks to one-year suggests that the glutamate modulating effect of evenamide could lead to a progressive and long-standing alteration in brain processes synergizing with the effect of antipsychotics to which the patient had become resistant. The above results, if replicated, would transform not only the management but also the societal outlook for patients with TRS."

[1] Lieberman et al, 1993; Andreasen et al, 2005

Commenting on these results, Professor John Kane, Professor of Psychiatry and Molecular Medicine, The Donald and Barbara Zucker School of Medicine, Hempstead New York, stated: "*Despite the fact that these results come from an open-label study performed largely in India, the continued improvement on all efficacy measures in TRS patients for one-year, together with the finding that approximately 50% of these patients improved to an extent that they no longer met criteria for TRS is highly encouraging. Furthermore, the finding that 25% of TRS patients achieved remission is very unexpected. These results should lead to expediting the conduct of a placebo-controlled international trial to replicate these results.*"

Efficacy and safety results from all 161 patients at the six-month timepoint of study 014/015 were announced in October 2023 (https://www.newron.com/news-and-media/regulatory-news/newron-trs-study-6-months-results-evenamide-substantially-improves).

Conference call

Newron's CEO Stefan Weber and CMO Ravi Anand will host a conference call today, January 4, 2024, at 3 pm CET/ 9 am ET.

The call can be accessed via the following dial-in numbers:

Switzerland/Europe:	+41 (0) 58 310 50 00
Germany:	+49 (0) 69 505 0 0082
United Kingdom:	+44 (0) 207 107 06 13
United States:	+1 (1) 631 570 56 13

Please dial in a few minutes early.

The presentation for this conference call can be downloaded as of today, January 4, 2024, at 7 am CET, on Newron's website (https://www.newron.com/investors/reports-and-presentation/year/2024). A replay of the conference call will be made available on Newron's website.

About remission

Remission is defined as a level of symptomology that does not interfere with an individual's behaviour and is also below that required for a diagnosis of schizophrenia. Symptom improvements should last for a significant period of time in order for remission to be reached. Individuals who achieve remission from schizophrenia have better subjective well-being and better functional outcomes indicating long-term wellness. Remission sets a standard for minimal severity of symptoms and signs and the duration of these symptoms and signs needs to remain at this minimal level. Remission represents the highest level of improvements that can be obtained in a patient with schizophrenia: remission in TRS patients has never been described before.

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, to explain the lack of benefit of most typical and atypical antipsychotics.

About study 014/015

Study 014 was a six-week, randomized, rater-blinded study being conducted at multiple sites in three countries (India, Italy and Sri Lanka). Study 014 has completed the enrollment of 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 were secondary objectives. Study 015 is the extension study that determined the long-term benefits of glutamate release inhibition. 121 of the 144 patients entered, completed the 1-year of treatment with evenamide. Considering the one-year treatment period (studies 014/015), 31 discontinued the study early, three of them due to adverse events, the other 28 due to withdrawal of consent or lost to follow up.

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 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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