Minerva Neurosciences Announces the Results of the Phase 3 Trial of Roluperidone for the Treatment of Negative Symptoms of Schizophrenia Following the Completion of the 40-Week Open-Label Extension

May 11, 2021

- ***Key results***
  - ***Continuous improvement in negative symptoms as measured by Positive and Negative Syndrome Scale (PANSS) Marder Negative Symptom Factor Score (NSFS) observed over one year (12-week double-blind and 40-week open-label periods) in patients receiving both 64 mg and 32 mg doses***
  - ***Continuous improvement in Personal and Social Performance (PSP) total score over one year, suggesting improvement in patients' everyday life functioning***
  - ***Favorable safety profile with few serious adverse events and no evidence of somnolence, extrapyramidal side effects or weight gain***
  - ***Limited number of relapses observed over one year***
- ***Results provide additional support for continued development of roluperidone and submission of NDA following completion of bioequivalence study and other work to address FDA comments from the Company's Type C meeting held on November 10, 2020***
- ***Findings to be discussed during Q1 2021 conference call and webcast on May 12, 2021, at 8:30 a.m.***

WALTHAM, Mass., May 11, 2021 (GLOBE NEWSWIRE) -- Minerva Neurosciences, Inc. (Nasdaq: NERV), a clinical-stage biopharmaceutical company focused on the development of therapies to treat central nervous system disorders, today announced results from the 40-week open-label extension (OLE) of its phase 3 trial of roluperidone for the treatment of negative symptoms (NS) of schizophrenia. The OLE followed the 12-week double-blind, placebo-controlled portion of this trial. During the OLE, both investigators and patients were blinded to the roluperidone dose received (see "About the trial" below).

Over the 40-week OLE period, 333 patients participated, of whom 166 patients received the 32 mg dose and 167 patients received the 64 mg dose. The mean improvement in negative symptoms was 6.8 points in the 32 mg arm and 7.5 points in the 64 mg arm. PSP total score improved by a mean of 12.3 points in the 32 mg arm and 14.5 points in the 64 mg arm, suggesting functional improvement.

The mean improvement in positive symptoms, as measured by the PANSS positive symptom subscore, was 1.9 points in the 32 mg arm and 1.8 points in the 64 mg arm.

Reduced emotional experience, as measured by a sub-factor of the NSFS that assesses a patient's motivation to take part in everyday life activities, had a mean improvement of 2.8 points in the 32 mg group and 3.0 points in the 64 mg group.

The relapse rate during the OLE, defined as patients being withdrawn from the trial due to worsening of symptoms of psychosis, was 15 patients out of 166 patients (9%) in the 32 mg arm and 10 patients out of 167 patients (6%) in the 64 mg arm. Over the one-year duration the relapse rate was 11.7% overall.

Roluperidone at both doses was safe and well tolerated, and treatment-emergent adverse events (TEAE) were generally mild to moderate in severity. The most frequently reported TEAE in the overall group of 333 patients that participated in the OLE were headaches in 26 patients (7.8%), followed by worsening of schizophrenia in 18 patients (5.4%) and insomnia in 15 patients (4.5%). No other TEAE was reported by more than 4% of the patients. There was one death (45 year old male) in the 64 mg arm due to treatment-unrelated respiratory failure that occurred after treatment discontinuation. Twenty patients (6%) experienced serious adverse events, with the majority of them associated with the disease characteristics, and only 5 were judged by the investigator to be related to roluperidone. In total, 37 patients (11%) did not complete the OLE due to TEAE, with 25 patients (7.5%) due to relapse-related events and the remaining 12 patients due to a variety of other TEAE reported in ≤1% of the patients. Few QT prolongations were observed during the OLE and were generally transient in duration, and only one in the 64 mg arm led to discontinuation from the study.

"I am delighted to announce that our one-year Phase 3 trial, now completed, supports our view that roluperidone, administered without concomitant treatment with antipsychotics, can potentially improve negative symptoms of schizophrenia and social functioning over the long term," said Dr. Luthringer. "We believe the data also suggest that roluperidone's unique pharmacology and mechanism of action potentially help to maintain the stability of psychotic symptoms over the duration of treatment.

"The encouraging new data reported today supplement our clinical database describing the effect of roluperidone for the treatment of negative symptoms of schizophrenia, which represent a significant unmet medical need for which there is currently no approved treatment in the U.S.," said Dr. Luthringer.

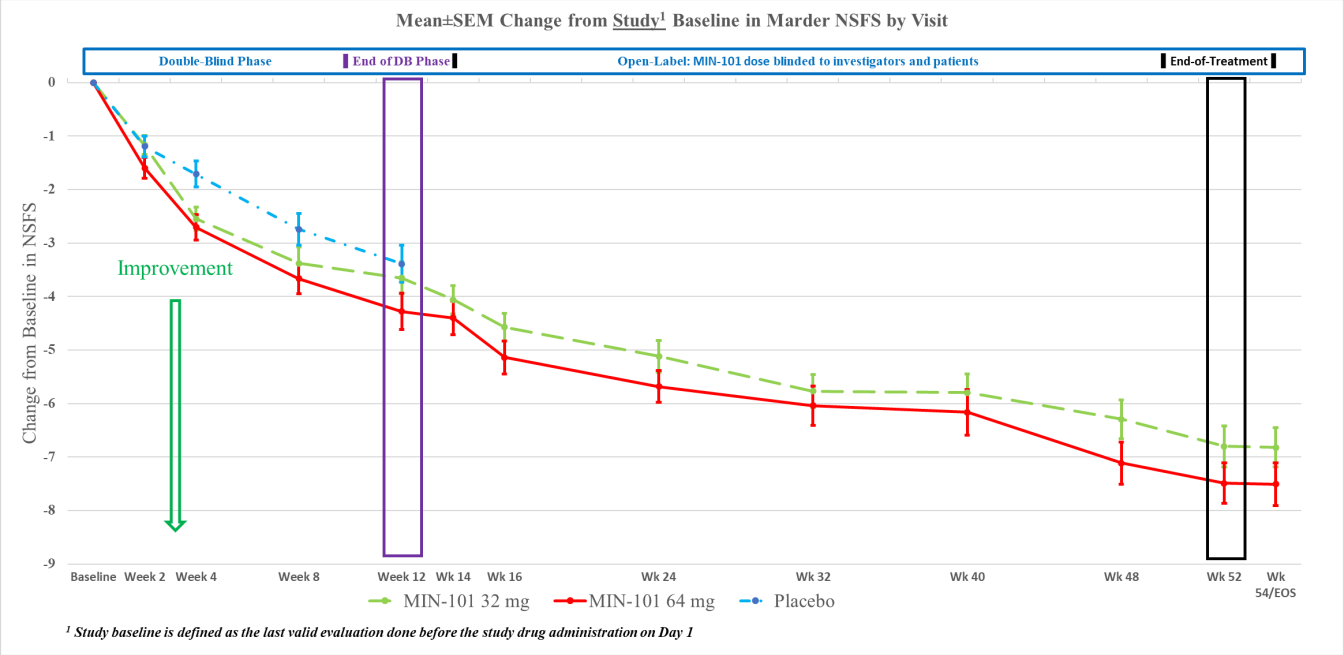
Summary of Phase 3 Key Efficacy Data

Table presenting mean±SD change in scores from start of roluperidone administration by duration of exposure

Endpoint	Placebo during 12-week double-blind phase (N=172)		32 mg for 12 months (DB+OLE) (N=107)	64 mg for 12 months (DB+OLE) (N=104)	Total 32 mg (N=166)	Total 64 mg (N=167)
	32 mg for 9 months (OLE) (N=59)	64 mg for 9 months (OLE) (N=63)				
NSFS	-4.5±3.50	-4.9±4.66	-6.3±4.00	-7.8±3.56	-6.8±3.94	-7.5±3.62
PSP Total Score	11.7±9.48	11.8±9.61	10.6±10.87	14.1±9.19	12.3±10.91	14.5±9.57
PANSS Positive Symptom Score	-1.3±1.98	-1.7±2.44	-1.8±3.96	-1.4±2.77	-1.9±3.53	-1.8±2.71
PANSS Total Score	-9.3±7.14	-12.5±8.66	-14.5±11.16	-15.2±8.73	-15.3±10.08	-16.0±8.17
Reduced Emotional Experience	-1.8±2.01	-2.1±1.87	-2.5±1.60	-3.2±1.66	-2.8±1.86	-3.0±1.62

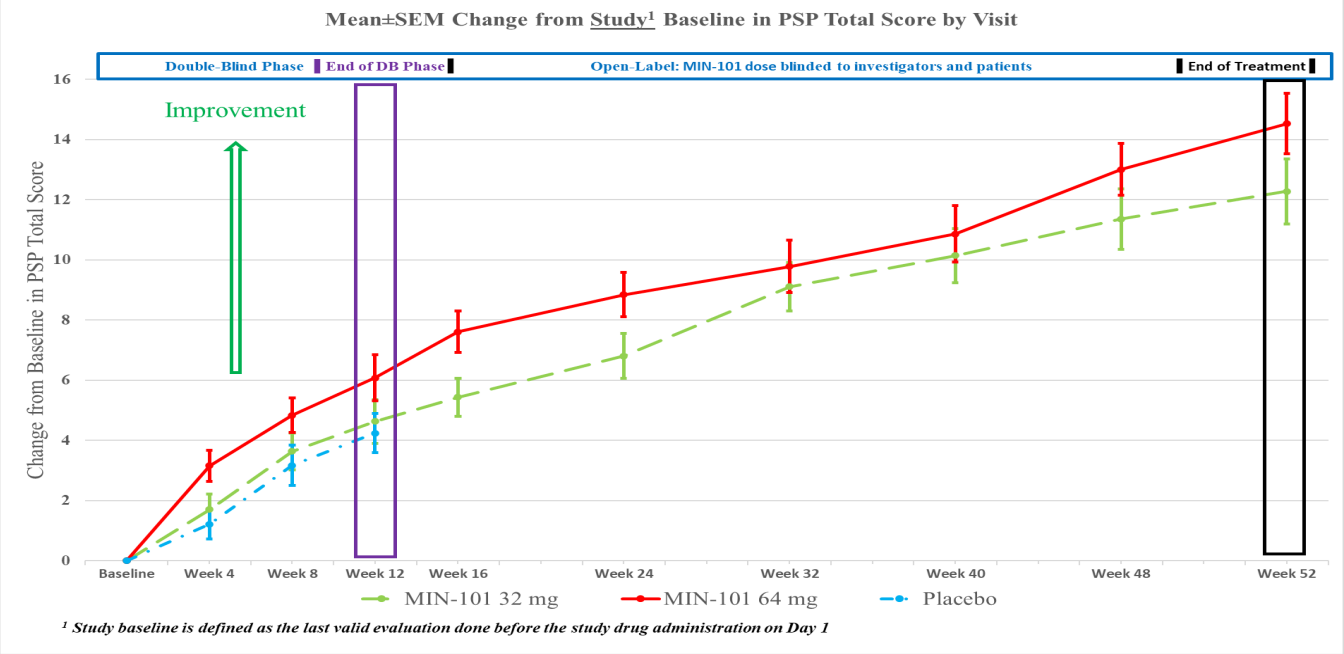
Note: DB= Double-Blind (12-week duration); OLE=Open-Label Extension (40-week duration)

NSFS



[1] Study baseline is defined as the last valid evaluation done before the study drug administration on Day 1

PSP



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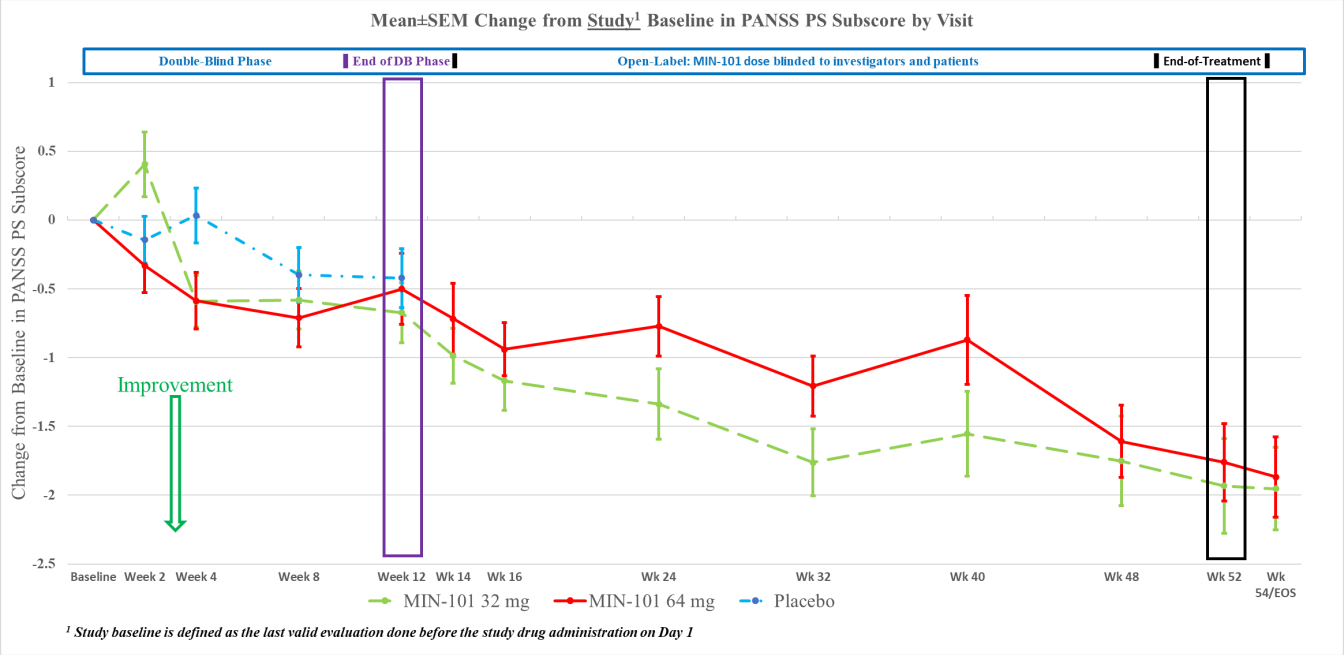
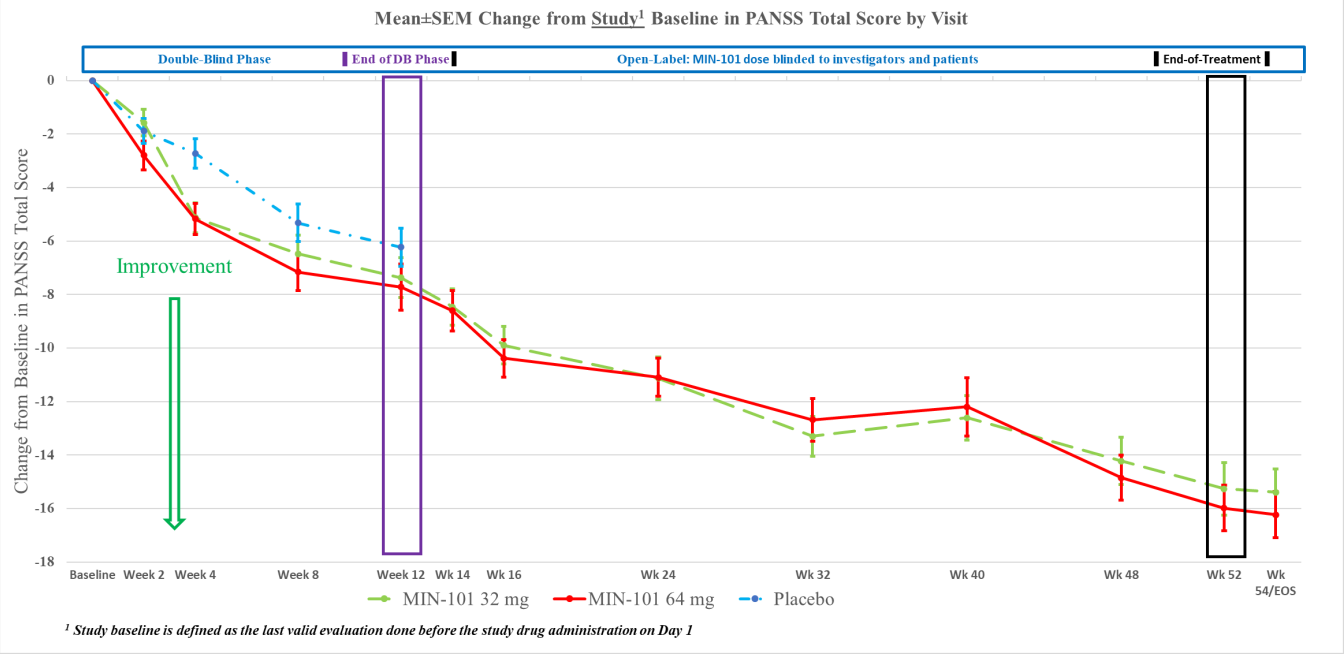
PANSS Positive Symptom Subscore



[1] *Study baseline is defined as the last valid evaluation done before the study drug administration on Day 1*

PANSS Total Score



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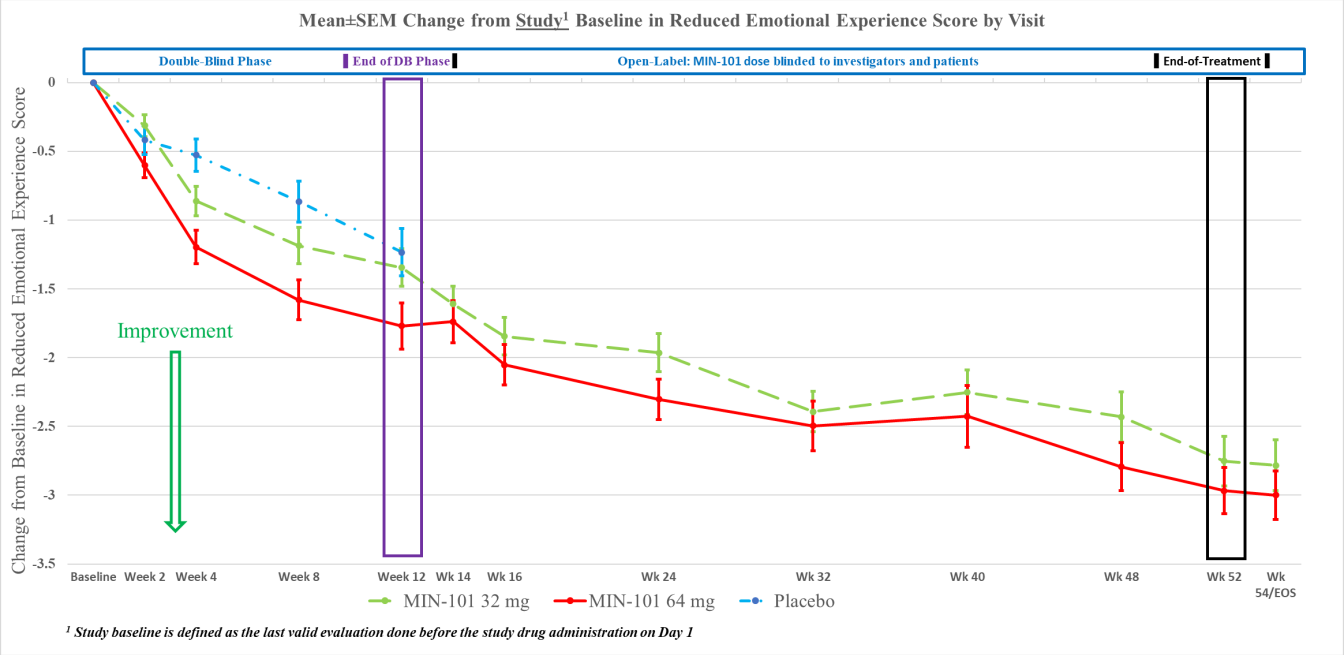
Reduced Emotional Experience



About the trial

In the double-blind, placebo-controlled portion of the Phase 3 trial, a total of 515 patients were randomized in a 1:1:1 ratio to 32 mg/day roluperidone, 64 mg/day roluperidone, or placebo for 12 weeks, and 513 patients received study drugs. Of these, 333 patients (65%) entered the 40-week OLE, where patients receiving roluperidone continued to receive the same dose of roluperidone, while patients who received placebo during the double-blind phase were randomized at the beginning of the study to receive either 32 mg or 64 mg during the OLE. A total of 166 patients were treated with the 32 mg dose, and 167 patients with the 64 mg dose. A total of 202 of the 333 patients entering the OLE (61%) completed the 40-week period. Both investigators and patients were blinded to the roluperidone doses throughout the OLE. The OLE was designed to evaluate the safety of roluperidone after long-term exposure. Efficacy endpoints were also assessed throughout the 12-month duration of the study. Data collected during the OLE are not placebo-controlled and therefore their interpretation is limited.

As announced on May 29, 2020, the 12-week double-blind, placebo-controlled portion of the trial did not meet its primary or key secondary endpoints in the intent-to-treat population. The 32 mg and 64 mg doses were not statistically significantly different from placebo at week 12 on the primary endpoint of NSFS ($p \leq 0.259$ and $p \leq 0.064$, respectively), or on the key secondary endpoint, PSP total score ($p \leq 0.542$ and nominal $p \leq 0.021$, respectively). The subsequent analysis of the change in baseline in NSFS and PSP total score based on the modified ITT population treated with the 64 mg dose resulted in nominally statistically significant $p \leq 0.044$ and $p \leq 0.017$, respectively.

Conference Call and Webcast Information

Minerva will discuss these results during its Q1 2021 conference call and webcast on Wednesday, May 12, 2021 at 8:30 a.m. EST. To participate, please dial (877) 312-5845 (domestic) or (765) 507-2618 (international) and refer to conference ID 8981662.

The live webcast can also be accessed under “Events and Presentations” in the Investors and Media section of Minerva’s website at ir.minervaneurosciences.com/. The archived webcast will be available on the website beginning approximately two hours after the event for 90 days.

Clinical trial background and data

Roluperidone has been tested to date in three clinical trials in patients suffering from schizophrenia. After a proof-of-concept trial in acutely relapsed schizophrenic patients that resulted in improvement of NS after treatment with roluperidone as compared to placebo, a confirmatory pivotal phase 2b trial was carried out in 2016. Results from this trial showed that roluperidone given as monotherapy (32 and 64 mg/day) induced a specific and significant improvement of NS (Davidson et al., 2017), with a limited number of relapses of psychotic symptoms during both the 12-week double-blind, placebo-controlled part of the study as well as during the 6-month OLE phase.

In addition to the specific improvement of NS, roluperidone in the phase 2b trial showed improvements in cognition as measured by the Brief Assessment of Cognition in Schizophrenia (BACS) scale (Keefe et al., 2018) as well as in functioning measured by the Personal and Social Performance (PSP) scale (Rabinowitz et al., 2019). Roluperidone was also shown to improve two key factors in negative symptom measurement, reduced emotional expression and experience (Harvey et al., 2020). Improvement in the two factors of the Brief Negative Symptom Scale (BNSS), anhedonia/avolition/asociality and expressivity (Kirkpatrick et al., 2018) were also demonstrated. Improvement in avolition was also shown to be a key driver of roluperidone’s efficacy (Strauss et al., 2020).

Based on the positive phase 2b results, the phase 3 trial was conducted. The results of the 12-week double-blind, placebo-controlled part of this study have been disclosed previously.

Pharmacology

Roluperidone has a novel and unique mechanism of action that has been shown to block serotonin, sigma, and α-adrenergic receptors that are all involved in the regulation of important brain functions, including mood, cognition, sleep and anxiety.

Roluperidone was designed to avoid a direct blockade of dopaminergic receptors (the key pharmacological target for first and second generation

antipsychotics), while maintaining blockade of a specific subtype of serotonin receptor called 5-HT_{2A} (an additional key target of second generation antipsychotics) as well as additional pharmacological targets (sigma$_2$ and adrenergic-α_{1A}).

Blockade of 5-HT_{2A}-receptors is believed to help control the positive symptoms of schizophrenia, such as hallucinations, delusions, agitation and thought and movement disorders (Geyer and Vollenweider, 2008). Additionally, blocking 5-HT_{2A} promotes slow wave sleep, a sleep stage often disrupted in patients with schizophrenia and linked to memory consolidation (Gronfier et al., 1996).

Roluperidone has also been shown to block sigma$_2$, which is involved in movement control, psychotic symptom control, learning and memory (Banister and Kassiou, 2012). Additionally, this mechanism is believed to support the improvement of negative symptoms.

α_{1A}-adrenergic receptor blockade is known to have synergistic effects with serotoninergic 5-HT_{2A} receptor blockade in controlling positive symptoms (Auclair et al., 2004; Maletic et al., 2017). The three neurotransmitter pathways affected by roluperidone are known to modulate dopaminergic, glutamatergic and GABAergic levels in the brain (Nakazawa and Saphota, 2019). Dysfunction in these pathways is believed to be play an important role in the onset of positive and negative symptoms, as well as cognitive impairments present in schizophrenia (Shukla et al., 2018).

About Schizophrenia and Negative Symptoms

Schizophrenia is a biologically and phenomenologically heterogeneous psychiatric condition, affecting between 0.7% and 1% (WHO, 2008; National Institute of Mental Health, 2015) of the world population.

Negative symptoms can be characterized by five constructs: blunted affect, alogia, avolition, anhedonia, and asociality (Marder and Galderisi, 2017).

The high personal and societal burden of negative symptoms in the clinical picture of schizophrenia has been acknowledged by the U.S. federal health authorities including NIMH, evidenced by the sponsored consensus meetings (Kirkpatrick et al., 2006; Marder et al., 2011; Marder et al., 2013).

Negative symptoms are the main cause of the poor functional outcome of patients suffering from schizophrenia (Harvey et al., 2017) and may also be one of the main reasons ultrahigh risk adolescents may develop full blown schizophrenia (Clark et al., 2016).

About Minerva Neurosciences

Minerva's portfolio of compounds includes: roluperidone (MIN-101), in clinical development for schizophrenia, and MIN-301, in pre-clinical development for Parkinson's disease. Minerva's common stock is listed on the Nasdaq Global Market under the symbol "NERV." For more information, please visit www.minervaneurosciences.com.

Forward-Looking Safe Harbor Statement

This press release contains forward-looking statements. Forward-looking statements are statements that are not historical facts, reflect management's expectations as of the date of this press release, and involve certain risks and uncertainties. Forward-looking statements include statements herein with respect to the timing and scope of future clinical trials and results of clinical trials with roluperidone (MIN-101); the clinical and therapeutic potential of this compound; the likelihood of successful clinical trials, regulatory review, commercialization, and future sales of and potential royalty stream from seltorexant; the timing and outcomes of future interactions with U.S. and foreign regulatory bodies; our ability to successfully develop and commercialize our therapeutic products; the sufficiency of our current cash position to fund our operations; and management's ability to successfully achieve its goals. These forward-looking statements are based on our current expectations and may differ materially from actual results due to a variety of factors including, without limitation, whether roluperidone will advance further in the clinical trials process and whether and when, if at all, it will receive final approval from the U.S. Food and Drug Administration or equivalent foreign regulatory agencies and for which indications; whether any of our therapeutic products or seltorexant will be successfully marketed if approved; whether any of our therapeutic product discovery and development efforts will be successful; management's ability to successfully achieve its goals; our ability to raise additional capital to fund our operations on terms acceptable to us; and general economic conditions. These and other potential risks and uncertainties that could cause actual results to differ from the results predicted are more fully detailed under the caption "Risk Factors" in our filings with the Securities and Exchange Commission, including our Annual Report on Form 10-K for the year ended December 31, 2020, filed with the Securities and Exchange Commission on March 8, 2021. Copies of reports filed with the SEC are posted on our website at www.minervaneurosciences.com. The forward-looking statements in this press release are based on information available to us as of the date hereof, and we disclaim any obligation to update any forward-looking statements, except as required by law.

Contact:

William B. Boni
VP, Investor Relations/
Corp. Communications
Minerva Neurosciences, Inc.
(617) 600-7376

Source: Minerva Neurosciences, Inc