Minerva Neurosciences Announces Results of Dose Escalation Study Evaluating Roluperidone (MIN-101) Administered at Supra-Therapeutic Doses in Healthy Volunteers

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- **Findings suggest expanded therapeutic window and significantly improved cardiovascular safety margin compared to formulation used in Phase 2b trial**

- **All doses tested up to 256 milligrams appear safe and well tolerated with no significant changes in cardiac repolarization and QTc intervals**

- **Tested formulation is used in ongoing Phase 3 trial**

- **Data to be reviewed at Minerva's roluperidone update and key opinion leader event on Tuesday, November 20, 2018 beginning at 8:00 a.m. Eastern Time in New York**

WALTHAM, Mass., Nov. 19, 2018 (GLOBE NEWSWIRE) -- Minerva Neurosciences, Inc. (NASDAQ: NERV), a clinical-stage biopharmaceutical company focused on the development of therapies to treat central nervous system (CNS) disorders, today announced the results from a prospective, double-blind, placebo-controlled, randomized single-escalating dose study in healthy subjects to evaluate the investigational drug roluperidone as monotherapy administered at nine ascending doses (16, 32, 64, 96, 128, 160, 192, 224 and 256 milligrams [mg]). The highest dose tested is 4 multiples of the highest dose (64 mg) being used in the ongoing Phase 3 trial with this compound, under development for the treatment of negative symptoms of schizophrenia.

The primary objectives of the study included the evaluation of the pharmacokinetics, dose-proportionality and the effect of plasma concentrations of roluperidone and its main metabolites on pharmacodynamic parameters using electrocardiogram (ECG) Fridericia-corrected QT interval (QTcF), a measurement of cardiac function. Secondary objectives included evaluation of safety and tolerability. A third objective was to provide an estimate of the supra-therapeutic dose to be used in the thorough QT study planned as part of the New Drug Application (NDA).

The trial included a total of 90 subjects. 72 received 7 different doses of roluperidone, and 18 received placebo. All subjects who were dosed completed the study as planned except for one male subject who received placebo and subsequently withdrew his consent.

Data from this trial demonstrated the following:

- The pharmacokinetics of roluperidone and its metabolites were dose proportional.
- No QTcF duration > 480 milliseconds (msec) or increases > 60 msec compared to baseline values were observed in any subject.
- 160 mg was the only roluperidone dose to show an adjusted QTcF mean increase from baseline of 10.7 msec. All other doses showed means -1.3 to 5 msec.
- No significant change in repolarization was observed.
- Two subjects (11%) in the placebo group and nine subjects (13%) in the roluperidone group reported adverse events that were mild to moderate in severity and resolved without sequelae.
- Doses up to 160 mg or 2.5 multiples of the highest dose being tested in the ongoing Phase 3 trial had no effect on any cardiac safety parameters.
- Slight but not clinically relevant increases in heart rate were observed in the placebo group and some of the roluperidone doses.
- No serious adverse events were reported.

Additional details will be presented at the Company's roluperidone update and key opinion leader event on Tuesday, November 20, 2018, 8:00 a.m., in New York. This event will be webcast, and institutional investors and analysts may RSVP to jporcelli@soleburytrout.com.

"We believe these findings suggest an expanded therapeutic window and a significantly improved safety margin for roluperidone," said Dr. Jay Saoud, Senior Vice President, Head of Research and Development at Minerva. "They provide further evidence that the formulation being used in the ongoing Phase 3 trial of roluperidone has a significantly reduced maximum concentration (C_{max}) of the metabolite known as BFB-520 when compared to the

formulation used in the Phase 2b trial, thereby reducing the potential of transient QTc increases at the doses currently tested in that Phase 3 trial.

“Furthermore, we believe these data suggest the potential for future testing of roluperidone in schizophrenic patients with an exacerbation of psychosis at higher doses than those being used in the Phase 3 trial,” said Dr. Saoud.

The Company had previously established the following in a study comparing the Phase 3 formulation and the Phase 2b formulation:

- Bioequivalent exposures of roluperidone as measured by area under the curve (AUC) for both the Phase 3 and Phase 2b trials (AUC is the main efficacy driver for the drug);
- Reduction of the C_{max} of BFB-520 by approximately 30% in the Phase 3 formulation compared to that used in Phase 2b, thus explaining the increased safety margin reported above;
- No observations of QTcF prolongations throughout the study;
- No observable food effect, thus allowing administration of the drug with or without food without changing its pharmacokinetic properties;
- Confirmation of the overall safety and tolerability profile of roluperidone.

The ongoing Phase 3 trial with roluperidone is a multicenter, randomized, double-blind, parallel-group, placebo-controlled, 12-week study to evaluate the efficacy and safety of 32 mg and 64 mg of roluperidone as monotherapy in adult patients with negative symptoms of schizophrenia. The 12-week study will be followed by a 40-week, open-label extension period during which patients on drug will continue receiving their original dose and patients on placebo will receive either 32 mg or 64 mg of roluperidone. Approximately 500 patients are expected to be enrolled at approximately 60 clinical sites in the U.S. and Europe. Top-line results from the 12-week double-blind phase of this trial are expected in mid-2019.

The previously announced Phase 2b trial with roluperidone achieved its primary endpoint, demonstrating a statistically significant benefit of the compound over placebo in improving negative symptoms[1,[2],[3]]. Roluperidone was reported to be well tolerated, and the incidence and types of side effects did not differ significantly between the roluperidone group and the placebo group. Unlike many currently marketed antipsychotic drugs, no metabolic adverse effects, no weight gain and no extra-pyramidal symptoms were observed.

About Roluperidone

Roluperidone is a drug candidate with equipotent affinities for 5-hydroxytryptamine-$_{2A}$ (5-HT_{2A}) and sigma2 and at lower affinity levels, α1-adrenergic receptors. Roluperidone exhibits no affinity for dopaminergic, muscarinic, cholinergic and histaminergic receptors. Roluperidone has no direct dopaminergic post-synaptic blocking effects, known to be involved in some side effects like extrapyramidal symptoms, sedation, prolactin increases and weight gain.

About Minerva Neurosciences:

Minerva Neurosciences, Inc. is a clinical-stage biopharmaceutical company focused on the development and commercialization of a portfolio of product candidates to treat CNS diseases. Minerva’s proprietary compounds include: roluperidone (MIN-101), in clinical development for schizophrenia; MIN-117, in clinical development for major depressive disorder (MDD); seltorexant (MIN-202 or JNJ-42847922), in clinical development for insomnia and MDD; 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 which are subject to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995, as amended. 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 current clinical trials and results of clinical trials with roluperidone (MIN-101); the timing and scope of future clinical trials and results of clinical trials with roluperidone; the clinical and therapeutic potential of roluperidone; 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 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 Quarterly Report on Form 10-Q for the quarter ended September 30, 2018, filed with the Securities and Exchange Commission on November 5, 2018. 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.

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[1] Davidson, M. et al., Efficacy and Safety of MIN-101: A 12-Week Randomized, Double-Blind, Placebo-Controlled Trial of a New Drug in Development for the Treatment of Negative Symptoms in Schizophrenia, 28 July 2017, https://doi.org/10.1176/appi.ajp.2017.17010122

[2] Kirkpatrick, B. et al., The brief negative symptom scale (BNSS): Sensitivity to treatment effects, Schizophr. Res. (2017), https://www.ncbi.nlm.nih.gov/pubmed/29275856

[3] Keefe, Richard et al., Cognitive effects of MIN-101 in patients with schizophrenia and negative symptoms: results from a randomized controlled trial: https://doi.org/10.4088/JCP.17m11753

Source: Minerva Neurosciences, Inc