NEWS RELEASE

Diffusion Pharmaceuticals Reports Final Results from Its Phase 1b Study of Trans Sodium Crocetinate in Hospitalized COVID-19 Patients

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CHARLOTTESVILLE, Va., May 10, 2021 (GLOBE NEWSWIRE) -- **Diffusion Pharmaceuticals Inc.** (NASDAQ: DFFN) ("Diffusion" or the "Company"), an innovative biopharmaceutical company developing novel therapies that enhance the body's ability to deliver oxygen to areas where it is needed most, today announced final results from the Phase 1b study evaluating trans sodium crocetinate (TSC) in hospitalized COVID-19 patients. Data from the open-label study were reviewed by an independent Safety Monitoring Committee (SMC).

Topline results based upon analyses of primary endpoint data from the trial were announced in February 2021, indicating that TSC was safe and well-tolerated when administered on a more frequent dosing regimen than previously tested in a clinical trial setting.

The Company and the SMC have concluded analyses of the trial's planned secondary and exploratory endpoints, which included time to improvement in WHO ordinal scale by day 7 and through day 29, time on oxygen supplementation, and hospital length of stay. While this study was not designed or powered to evaluate efficacy, the Company and SMC observed that patients receiving the 1.5 mg/kg dose had improved outcomes in these secondary and exploratory endpoints compared to those receiving lower doses. In addition, no patients required dialysis or developed acute kidney injury and there were no reports of pulmonary embolism or deep vein thrombosis. One death was reported during the study, a patient who received the lowest dose and which was determined by the SMC to be not drug related.

The SMC went on to recommend the Company consider additional preliminary work before initiating a registrational study, including the testing of higher TSC doses and a continuous intravenous infusion. Of note, the first of the Company's three planned Oxygenation Trials, the TCOM study, tested TSC at doses up to 2.5 mg/kg.

"We learned a lot from this safety and tolerability trial, not only is TSC safe with more frequent dosing, but across a wider range of doses than previously tested. We are encouraged by the trends in the data suggesting TSC improved relevant clinical outcomes, recognizing the conclusions we can draw are limited due to the study not being designed or powered to evaluate efficacy" said Chris Galloway, M.D., Chief Medical Officer. "We believe the observations and recommendations of the SMC further support the importance of our three, small, controlled Oxygenation Trials as efficient means to demonstrate TSC's enhancement of oxygenation with more clarified dosing and, if successful, allowing us to design later phase trials to support commercially-focused development in specific indication(s)."

Trial Design

- The trial enrolled 24 patients divided into four sequential cohorts of six patients, with each patient in a dose cohort receiving the same intravenous doses of 0.25 mg/kg, 0.5 mg/kg, 1.0 mg/kg, or 1.5 mg/kg, depending on the patient's cohort.
- All patients were administered intravenous doses of TSC every six hours for a minimum of five days and up to 15 days.

"This study of TSC in COVID-19 patients was initiated to determine if TSC is safe and well tolerated when given in multiple doses per day in a patient population suffering from an acute respiratory infection. The medical and scientific communities have since come to understand COVID-19 is a much more complex disease, and the study itself was complicated to conduct. So, we are very happy the trial achieved its primary objective, demonstrating safety and tolerability, and the results of the secondary endpoint analyses confirm our belief in the value of executing our ongoing Oxygenation Trials," said Robert Cobuzzi, Jr., Ph.D., President and CEO of Diffusion.

Near-Term Clinical Strategy

Diffusion has initiated a series of three short-term Oxygenation Trials in the United States in 2021, funded with cash-on-hand. The first of these studies, the TCOM Trial, initiated, enrolled, and completed dosing in March 2021.

- TCOM Trial: This trial was a randomized, double-blind, placebo controlled, pharmacokinetic and pharmacodynamic study of TSC that enrolled and dosed 30 healthy volunteers. Trial participants were randomized into one of six subgroups, each of which received a single intravenous dose of placebo or one of five different doses of TSC ranging from 0.5 mg/kg to 2.5 mg/kg. All trial participants received supplemental

oxygen during equivalent monitoring periods before and after TSC or placebo was administered while being continuously monitored with TCOM sensors applied to the lower extremity. The primary endpoint evaluates the relative change in TCOM readings from baseline after TSC administration. Diffusion anticipates that the ongoing collection and analyses of the TCOM trial data will be completed and announced by the end of the second quarter of 2021.

- Induced Hypoxia Trial: This trial will be a double-blind, randomized, placebo-controlled study which will evaluate the effects of TSC on maximal oxygen consumption, or VO2, and partial pressure of blood oxygen, or PaO2, in normal healthy volunteers subjected to incremental levels of physical exertion while exposed to hypoxic and hypobaric conditions (i.e., simulated altitude). The study will be statistically powered to evaluate the difference in effect of TSC versus placebo on oxygen availability and consumption.
- DLCO Trial: This trial will be a double-blind, randomized, placebo-controlled study which will evaluate the effects of TSC on the diffusion of carbon monoxide through the lungs (DLCO) in patients with previously diagnosed interstitial lung disease who have a baseline DLCO test result that is abnormal. DLCO will act as a surrogate measure of oxygen transfer efficiency, or uptake, from the alveoli of the lungs, through the plasma, and onto hemoglobin within red blood cells. The study will be statistically powered to evaluate the difference in effect of TSC versus placebo on improvement in DLCO.

Diffusion anticipates initiating and completing the DLCO Trial and Induced Hypoxia Trial in the second half of 2021, with topline results from each study available within two months of their respective completion. The Company believes positive data from any one or more of the three Oxygenation Trials, if obtained, would provide evidence of a definitive effect of TSC on oxygenation. If such positive data are obtained, the Company expects to announce in the fourth quarter of 2021 the hypoxia-related indications in which TSC would be studied as part of its clinical development strategy aimed at supporting regulatory approval and commercialization. Diffusion intends to initiate clinical studies in the identified indications during the first quarter of 2022.

About Diffusion Pharmaceuticals Inc.

Diffusion Pharmaceuticals Inc. is an innovative biopharmaceutical company developing novel therapies that enhance the body's ability to deliver oxygen to areas where it is needed most. Diffusion's lead product candidate, TSC, is being developed to enhance the diffusion of oxygen to tissues with low oxygen levels, also known as hypoxia, a serious complication of many of medicine's most intractable and difficult-to-treat conditions. In addition to TSC, Diffusion's product candidate DFN-529, a novel, allosteric PI3K/Akt/mTOR Pathway inhibitor, is in early-stage development. For more information, please visit us at **www.diffusionpharma.com**.

Forward-Looking Statements

This press release includes express and implied forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including regarding the Company's near-term strategic priorities, anticipated timelines for the initiation, completion, and announcement of data from the Company's ongoing and planned oxygenation trials, and the potential therapeutic value of TSC. The Company may, in some cases, use terms such as "believes," "estimates," "anticipates," "expects," "plans," "intends," "may," "could," "might," "will," "should," "approximately," or other words that convey uncertainty of future events or outcomes to identify these forward-looking statements. Although the Company believes that it has a reasonable basis for each forward-looking statement contained herein, forward-looking statements by their nature involve risks and uncertainties, known and unknown, many of which are beyond the Company's control, and as a result the Company's actual results could differ materially from those expressed or implied in any forward-looking statement. Particular risk and uncertainties include, among other things, those related to: the Company's ability to design, initiate, enroll, execute, and complete its ongoing and planned studies evaluating TSC; general economic, political, business, industry, and market conditions, including the ongoing COVID-19 pandemic; and the other factors discussed under the heading "Risk Factors" in the Company's filings most recent Annual Report on Form 10-K and other filings with the U.S. Securities and Exchange Commission. Any forward-looking statements in this press release speak only as of the date hereof (or such earlier date as may be identified) and, except as required by applicable law, rule, or regulation, the Company undertakes no obligation to update any such statements after the date hereof.

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