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Cara Therapeutics Announces Positive Data From Quantitative Phase 1 Trial Measuring Respiratory Safety of I.V. CR845

- I.V. CR845 statistically equivalent to placebo across all measures of respiratory safety -

STAMFORD, Conn., April 24, 2017 (GLOBE NEWSWIRE) -- Cara Therapeutics, Inc. (Nasdaq:CARA), a biopharmaceutical company focused on developing and commercializing new chemical entities designed to alleviate pain and pruritus by selectively targeting peripheral kappa opioid receptors, today announced summary results from its Phase 1 safety trial showing that I.V. CR845 did not significantly differ from placebo across three quantitative measures of respiratory drive in healthy individuals. Respiratory depression remains the most life-threatening side effect of traditional, centrally acting, opioid analgesics, the most commonly used drug class for current treatment of postoperative pain in the United States.

"We are very pleased that I.V. CR845 demonstrated no significant alteration in any measure of respiratory drive, even at doses five-fold greater than the projected therapeutic dose," said Joseph Stauffer, D.O., M.B.A., Chief Medical Officer of Cara Therapeutics. "These data further underscore the overall clinical safety profile of CR845 for use in postoperative pain management and continue to differentiate it from traditional mu opioids."

"There remains a clear unmet need for effective analgesic agents that lack the risk of serious, potentially fatal respiratory depression that is inherent in current opioids," said Christopher Wu, M.D., Department of Anesthesiology and Critical Care, Johns Hopkins University. "The ability to administer I.V. CR845 without any direct effect on respiratory function is a significant advantage in the acute post-surgical care setting where patients are already at heightened risk of respiratory depression. CR845's profile also aligns with the most recent standard of care guidelines for postoperative pain, which call for minimizing opioid-related side effects."

Respiratory Safety Phase 1 Trial Design and Results

The Phase 1 trial was a randomized, double-blind, placebo-controlled, three-way crossover trial of two doses of I.V. CR845 (1.0 ug/kg, and 5.0 ug/kg) versus placebo on three measures of respiratory drive in 15 healthy volunteers. Each subject was randomized to one of three treatment sequences and was administered I.V. bolus placebo, CR845 (1.0 ug/kg) and CR845 (5.0 ug/kg) on sequential 24-hour periods, with CR845 at 5.0 ug/kg representing a projected five-fold supra-therapeutic dose. After each administration, and continuing through four hours post-dosing, end-tidal CO2 (ETCO2), oxygen saturation (SpO2) and respiratory rate were continuously monitored. The primary safety endpoints were: a > 10 mmHg sustained (> 30 seconds duration) increase in ETCO2 above baseline or to > 50 mmHg, and a sustained reduction in SpO2 to < 92 percent.

Mean ETC02 pre-dosing ranged from 36.1 ± 3.9 to 37.8 ± 2.9 mmHg across treatment groups. At one hour post-administration, ETC02 values for placebo, CR845 1.0 ug/kg and CR845 5.0 ug/kg treatment groups were numerically and statistically equivalent at 38.1 ± 2.8, 38.1 ± 3.1, and 38.3 ± 2.9 mmHg, respectively. Pre-treatment levels of SpO2 ranged from 98.3 percent ± 1.2 to 98.9 percent ± 1.0 and were measured at 97.8 percent ± 1.2, 98.2 percent ± 1.5 and 97.9 percent ± 1.0 for placebo, CR845 1.0 ug/kg and CR845 5.0 ug/kg treatment groups respectively, at one hour post-treatment. There were no statistically significant differences in any respiratory measures between groups throughout the four-hour observation period and no individual patient met the threshold for a respiratory safety event.

All reported treatment-emergent adverse events were previously reported with CR845 administration and were mild, resolving without intervention.

An oral presentation of this dataset will be part of the Journal *Anesthesiology* Symposium on Sunday, October 22, 2017 at the American Society of Anesthesiology (ASA) Annual Meeting in Boston, MA.

About Respiratory Depression

Respiratory depression is the most life-threatening side effect of conventional opioids, which act primarily at the mu opioid receptor subtype. Mu opioid receptors are present in high amounts in brainstem areas that control respiration, similar to midbrain and spinal areas that regulate pain perception. A wide variety of factors are involved in determining the effects of mu opioids on breathing, with high potency and speed of onset being well known risk factors, in addition to the presence of

sedating medications, the site of surgery and surgical technique used, the presence of underlying disease, and the patient's age, sex, genetics, and hormonal status, as well as arousal and pain, which can vary substantially between patients. Although death rates from opioid-induced respiratory arrest have declined in many hospitals due to more aggressive patient monitoring, it remains the leading concern of anesthesiologists and pain specialists (1). However, such monitoring is generally not available when patients are discharged home with powerful opioids, and the increasingly high rate of deaths associated with both opioid use and misuse is presently considered a national health crisis.

(1) Safe use of opioids in hospitals. *Sentinel Event Alert*, 2012 Aug 8;(49):1-5

https://www.jointcommission.org/assets/1/18/SEA_49_opioids_8_2_12_final.pdf

About the Ongoing CLIN3001 Postoperative Pain Trial

The CLIN3001 Phase 3 trial is a multi-center, randomized, double-blind, placebo-controlled, parallel-group adaptive design trial with repeated doses of I.V. CR845 or placebo administered both prior to and following abdominal surgery in male and female patients. The trial is enrolling up to 450 patients at 30 clinical sites within the U.S. Two doses of I.V. CR845 (1.0, and 0.5 ug/kg I.V.) are being compared to placebo. The primary efficacy measure is the Change in Pain Intensity over the 24-hour post-operative period (AUC-24) using the patient-reported Numeric Rating Scale (NRS) score collected at pre-specified time points through 24 hours. Postoperative nausea and vomiting (PONV) will be evaluated as a secondary efficacy measure.

An interim conditional power assessment at approximately 65 percent patient recruitment completion will read out in the second quarter of 2017.

About CR845

CR845 is a peripherally acting kappa opioid receptor agonist currently in development for the treatment of acute and chronic pain and pruritus. In multiple randomized, double-blind, placebo-controlled Phase 2 trials in patients undergoing laparoscopic hysterectomy or bunionectomy procedures, I.V. CR845 treatment resulted in statistically significant reductions in pain intensity and opioid-related side effects. In more than 1200 subjects dosed to date, CR845 was observed to be well-tolerated, without incurring the dysphoric and psychotomimetic side effects that have been reported with centrally acting (CNS-active) kappa opioid receptor agonists, and lacking the respiratory depression and abuse liability of mu opioid receptor agonists. Top-line data from a Phase 2b trial of Oral CR845 in chronic pain associated with osteoarthritis are expected in the second quarter of 2017.

About Cara Therapeutics

Cara Therapeutics is a clinical-stage biopharmaceutical company focused on developing and commercializing new chemical entities designed to alleviate pain and pruritus by selectively targeting peripheral kappa opioid receptors. Cara is developing a novel and proprietary class of product candidates, led by CR845, that target the body's peripheral nervous system and have demonstrated initial efficacy in patients with moderate-to-severe pain without inducing many of the undesirable side effects typically associated with currently available pain therapeutics.

Forward-looking Statements

Statements contained in this press release regarding matters that are not historical facts are "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. Examples of these forward-looking statements include statements concerning the expected timing of the read out of the planned interim conditional power assessment of the ongoing CLIN3001 postoperative pain trial of I.V. CR845 and the expected timing of the release of top-line data from the ongoing Phase 2b trial of Oral CR845 in chronic pain associated with osteoarthritis Because such statements are subject to risks and uncertainties, actual results may differ materially from those expressed or implied by such forward-looking statements. Risks are described more fully in Cara's filings with the Securities and Exchange Commission, including the "Risk Factors" section of Cara's Annual Report on Form 10-K for the year ended December 31, 2016 and its other documents subsequently filed with or furnished to the Securities and Exchange Commission. All forward-looking statements contained in this press release speak only as of the date on which they were made. Except to the extent required by law, Cara undertakes no obligation to update such statements to reflect events that occur or circumstances that exist after the date on which they were made.

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