October 29, 2013

Cara Therapeutics Reports Positive Results from Phase 2 Clinical Trial I.V. CR845, for Post-Operative Pain Following Bunionectomy

Cara Therapeutics Reports Positive Results from Phase 2 Clinical Trial I.V. CR845, for Post-Operative Pain Following Bunionectomy

SHELTON, Conn., Oct. 29, 2013 /PRNewswire -- Cara Therapeutics, Inc. today announced top-line results from a Phase 2 clinical trial of its novel, peripherally-acting kappa opioid receptor agonist, I.V. CR845, for the treatment of acute pain following bunionectomy. In a pre-specified analysis for patients who completed the trial ("Completer Analysis"), repeat dosing of I.V. CR845, over 48 hours post-surgery, provided statistically greater pain reduction than placebo at both the 24 and 48 hour time points following initiation of treatment, as assessed using the FDA recommended endpoint, the Summed Pain Intensity Difference (SPID).

SHELTON, Conn., Oct. 29, 2013 /PRNewswire -- Cara Therapeutics, Inc. today announced top-line results from a Phase 2 clinical trial of its novel, peripherally-acting kappa opioid receptor agonist, I.V. CR845, for the treatment of acute pain following bunionectomy. In a pre-specified analysis for patients who completed the trial ("Completer Analysis"), repeat dosing of I.V. CR845, over 48 hours post-surgery, provided statistically greater pain reduction than placebo at both the 24 and 48 hour time points following initiation of treatment, as assessed using the FDA recommended endpoint, the Summed Pain Intensity Difference (SPID).

The Phase 2 trial, referred to as CLIN2003, was a randomized, double-blind, placebo-controlled trial of I.V. CR845 (0.005 mg/kg/dose) in 51 women and men undergoing a primary unilateral first-metatarsal bunionectomy surgery at a single site in the United States. Patients received an initial bolus dose of I.V. CR845 or placebo at randomization, and again, at the patient's request, 30-60 minutes later, and thereafter, as needed, up to every 8 hours (until hour 40) over a 48-hour dosing period. Fentanyl was available as "rescue" medication for any patient not reporting adequate pain relief. In the Completer Analysis, the I.V. CR845 treatment arm met the trial's primary endpoint of a statistically significant reduction in pain intensity, as measured by the SPID score, over the initial 24 hour time period (SPID0-24; $p<0.05$) compared to placebo. The I.V. CR845 treatment arm also met the secondary endpoint of a statistical reduction in pain intensity over the entire 48-hour dosing period (SPID0-48; $p<0.025$).

In addition, I.V. CR845 treatment resulted in a statistically significant reduction in the incidence of opioid-related adverse events of nausea and vomiting (by 60% and 80%, respectively; $p<0.05$) compared to placebo during the 48 hour period of treatment. Fentanyl was available to both I.V. CR845 and placebo treatment groups upon patient request throughout the trial. There were no observed differences in the overall mean fentanyl use between the placebo and I.V. CR845 treatment groups.

"We believe that these Phase 2 bunionectomy data represent the first clinical demonstration that a kappa opioid receptor agonist is effective for the treatment of hard tissue pain. Previous clinical trials with kappa opioids have focused on soft tissue, primarily visceral pain," said Derek Chalmers, Ph.D., D.Sc., President and CEO at Cara. "The results of this trial, together with our previously reported positive Phase 2 data in laparoscopic hysterectomy, are indicative of I.V. CR845's broad and robust analgesic potential and will form the basis for our planned pivotal Phase 3 trials with I.V. CR845," said Dr. Chalmers.

About CR845

CR845 is a peripherally-acting kappa opioid receptor agonist currently in development for the treatment of acute and chronic pain. I.V. CR845 treatment resulted in statistically significant reductions in pain intensity and narcotic use in a previously completed double-randomized, double-blind, placebo-controlled Phase 2b trial of I.V. CR845 (0.04mg/kg/dose) in women undergoing a laparoscopic hysterectomy. This trial was conducted at 22 sites across the United States, and enrolled 203 patients who were randomized into four treatment arms: (1) both a pre-and a post-operative dose of CR845; (2) a single pre-operative dose of CR845; (3) a single post-operative dose of CR845; and (4) both pre- and post-operative placebo. Patients receiving both a pre- and post-operative dose of CR845 exhibited a statistically significant reduction (~33%, $p<0.05$) of morphine use over 24 hours compared to the placebo group. This patient group also exhibited an approximately two-fold (~100%) increase in their calculated 24 hour PID0-24 ($p=0.002$) and SPID0-24 ($p=0.003$) values compared to placebo-treated subjects. Significant 24-hour analgesic effects were also seen in patients receiving a single post-operative dose of CR845 where SPID0-24 values ($p=0.014$) increased by more than 50% when compared to placebo. Patients receiving CR845 also

exhibited statistically significant reductions in nausea and vomiting.

In addition to the development of I.V. CR845 for hospital use, Cara has also completed a successful Phase 1 trial of an oral capsule formulation of CR845, or Oral CR845, and plans to enter Phase 1 trials with a tablet formulation of Oral CR845 in the first half of 2014. Cara believes a tablet formulation of Oral CR845 could be used to provide pain relief for hospital patients being prepared for discharge, as well as address a significant unmet medical need for a safer, non-abusable alternative to narcotic opioids and NSAIDs for the treatment of moderate-to-severe acute and chronic pain. CR845 has been found to be safe and well tolerated in the more than 300 patients dosed to date, with no cases of dysphoric or psychotomimetic side effects that have been reported with centrally-acting kappa opioid receptor agonists.

About Cara Therapeutics

Cara Therapeutics is a privately held clinical-stage biopharmaceutical company focused on developing and commercializing new chemical entities designed to alleviate pain by selectively targeting kappa opioid receptors. Cara is developing a novel and proprietary class of product candidates with a peripheral mechanism of action that has demonstrated efficacy in patients with moderate-to-severe pain without inducing many of the undesirable side effects typically associated with currently available pain therapeutics. Cara's most advanced product candidate, intravenous, or I.V., CR845, has demonstrated significant pain relief and a favorable safety and tolerability profile in three Phase 2 clinical trials in patients with acute postoperative pain. Cara plans to begin Phase 3 registration trials for I.V. CR845 in the second half of 2014. Cara is also developing an oral version of CR845, or Oral CR845, for acute and chronic pain, for which it has successfully completed a Phase 1 clinical trial to establish oral bioavailability parameters.

Forward-Looking Statements

Certain statements in this press release are forward-looking statements that involve a number of risks and uncertainties. Such forward-looking statements include statements relating to the therapeutic applications of I.V. and Oral CR845 and about Cara's strategy, technologies and clinical programs, and ability to identify and develop drugs, as well as other statements that are not historical facts. Actual events or results may differ materially from Cara's expectations. Factors that could cause actual results to differ materially from the forward-looking statements may include, but are not limited to, the timing, success and cost of Cara's research and clinical studies and Cara's ability to obtain additional financing. These forward-looking statements represent Cara's judgment as of the date of this release. Cara disclaims any intent or obligation to update these forward-looking statements.

Contact: Derek Chalmers President & CEO Cara Therapeutics, Inc. +1-203-567-1500

SOURCE: Cara Therapeutics, Inc.