Cara Therapeutics Reports Positive Top-Line Data from Adaptive Phase 2/3 Trial of I.V. CR845 in Patients Undergoing Abdominal Surgery

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-I.V. CR845 achieved statistical significance for the study's primary endpoint of pain relief over the 0 to 24-hour (AUC 0-24) period post-surgery for combined surgeries at the 1.0 mcg/kg dose (p=0.032)-

-I.V. CR845 treatment resulted in statistically significant reductions in the secondary endpoint of incidence of nausea and vomiting at 24-hours post-surgery for both the 0.5 and 1.0 mcg *doses (p=0.006; p<0.0001 respectively)-*

-Cara to host conference call today at 8:30 a.m. EDT-

STAMFORD, Conn., June 27, 2018 (GLOBE NEWSWIRE) -- Cara Therapeutics, Inc. (Nasdaq:CARA), a biopharmaceutical company focused on developing and commercializing new chemical entities designed to alleviate pruritus and pain by selectively targeting peripheral kappa opioid receptors, today announced positive top-line data from the adaptive Phase 2/3 trial of I.V. CR845 in patients undergoing abdominal surgeries. At the 1.0 mcg/kg dose, I.V. CR845 demonstrated statistically significant reductions in pain intensity compared to placebo at all pre-specified post-operative periods of 0-6 hours (p=0.001); 0-12 hours (p=0.004); 0-18 hours (p=0.013); and 0-24 hours (p=0.032). Additionally, I.V. CR845 treatment resulted in statistically significant reductions in the incidence of post-operative nausea and vomiting over the 24-hour period post-surgery for both 0.5 and 1.0 mcg/kg doses (p=0.006; p<0.0001, respectively).

"We are very pleased that these data demonstrate the overall benefit of I.V. CR845 in both providing pain relief across surgery types up to 24 hours post-surgery and reducing post-operative nausea and vomiting, a significant medical need in the post-operative setting," said Derek Chalmers, Ph.D., D.Sc., President and Chief Executive Officer of Cara Therapeutics. "As there continues to be a critical need for new post-surgical analgesics like I.V. CR845 that lack abuse potential and traditional mu opioid side effects, we will be assessing all options, including discussions with regulators, as to how to best move this program forward."

"The current practice of perioperative pain management anchored around traditional opioids often results in frequent opioid-related adverse events, such as nausea and vomiting, which can be debilitating and delay patients' post-surgical recovery," said Sabry Ayad, M.D., Professor of Anesthesiology, Anesthesiology Institute, Cleveland Clinic and one of the study's investigators. "The ability of I.V. CR845, under standard of care conditions in the present trial, to provide not only additional pain relief but also a considerable decrease in the incidence and degree of post-operative nausea and vomiting underscores the potential of I.V. CR845 to provide meaningful clinical benefit in the immediate post-operative recovery period."

Phase 2/3 Trial Design and Top-Line Data

The adaptive Phase 2/3 trial was a randomized, double-blind, placebo-controlled trial designed to evaluate the analgesic efficacy and safety of two doses of I.V. CR845 (0.5 mcg/kg and 1.0 mcg/kg) versus placebo given at pre-specified intervals pre- and post-surgery in 444 patients undergoing abdominal surgery, composed of 228 patients who underwent ventral hernia surgery and 216 patients who completed a hysterectomy procedure. Patients received a 2X loading dose of I.V. CR845 pre-surgery and four additional doses given at 0, 6, 12 and 18 hours after surgery. The primary endpoint was pain relief as measured by Area Under the Curve (AUC) of the Numerical Rating Scale (NRS) pain intensity scores collected over the first 24-hour period after the baseline dose (0 hour) post-surgery for all combined surgeries. In addition to safety, the secondary endpoints included incidence of vomiting, improvement in impact scores of post-operative nausea and vomiting (PONV), reduction in use of rescue analgesic medication, as well as patient global assessment at 24 hours post baseline dose after surgery.

- I.V. CR845 achieved statistical significance for the primary endpoint of pain relief over 24 hours (AUC 0-24) post-surgery with the 1.0 mcg/kg dose versus placebo (p=0.032) and also demonstrated statistical significance across two additional pre-specified sensitivity analyses for pain relief (p=0.040 and p=0.041) for the same period post-surgery. The 0.5 mcg/kg dose did not achieve statistical significance over the 0-24 hour period (p=0.076). In addition, improvement in pain AUC was statistically significant for both the 0.5 and 1.0 mcg/kg doses over 0 to 6 hours (p=0.041, p=0.001) and 0 to 12 hours (p=0.035, p=0.004) periods and also statistically significant for the 1.0 mcg/kg dose over the 0 to 18-hour period (p=0.013) post-surgery.
- At 6 and 24 hours after baseline dose post-surgery, there were statistically significant improvements in PONV impact scores with both doses of I.V. CR845 compared to placebo: 0.5 mcg/kg (6 hrs.: p=0.0072, 24 hrs.: p<0.006) and 1.0 mcg/kg (6 hrs.: p<0.0001, 24 hrs.: p<0.0001).
- There were statistically significant differences between placebo and both doses of CR845 with respect to the total use of anti-emetic medication over the first 24 hours post-surgery (0.5 mcg/kg: p=0.0003; 1.0 mcg/kg: p< 0.0001). The percentage of patients who did not take any anti-emetic medication over 24 hours was 56% for placebo compared to 70% for CR845 0.5 mcg/kg and 81% for CR845 1.0 mcg/kg.
- There was a 73% reduction in the incidence of patient-reported vomiting in the group receiving the 1.0 mcg/kg dose versus placebo (p=0.029). Although the 0.5 mcg/kg also showed reduction in vomiting, it did not reach statistical significance.

- Both doses of I.V. CR845 exhibited numerical trends toward reduced use of rescue analgesic medication compared to placebo, but did not achieve statistical significance. There was no significant effect, compared to placebo, on patient's global assessment of medication for either dose of I.V. CR845 over the 24-hour period.
- Common adverse effects reported in the placebo and both I.V. CR845 groups were generally low and similar in incidence, and included nausea, constipation, vomiting, flatulence, headache and dyspepsia.

The full results of this trial will be presented at a future scientific or medical conference.

Conference Call

Cara management will host a conference call today at 8:30 a.m. EDT to discuss the data. To participate in the conference call, please dial (855) 445-2816 (domestic) or (484) 756-4300 (international) and refer to conference ID 3863718. A live webcast of the call can be accessed under "Events and Presentations" in the News & Investors section of the Company's website at www.CaraTherapeutics.com.

An archived webcast recording will be available on the Cara website beginning approximately two hours after the call.

About Cara Therapeutics

Cara Therapeutics is a clinical-stage biopharmaceutical company focused on developing and commercializing new chemical entities designed to alleviate pruritus and pain by selectively targeting peripheral kappa opioid receptors (KORs). Cara is developing a novel and proprietary class of product candidates, led by KORSUVA™ (CR845/difelikefalin), a first-in-class KOR agonist that targets the body's peripheral nervous system, as well as certain immune cells. In Phase 2 trials, KORSUVA injection has demonstrated statistically significant reductions in itch intensity and concomitant improvement in quality of life measures in hemodialysis patients with moderate-to-severe chronic kidney disease-associated pruritus (CKD-aP), and is currently being investigated in Phase 3 trials in hemodialysis patients with CKD-aP. Cara is partnered with Vifor Fresenius Medical Care Renal Pharma Ltd. (VFMCRP) to commercialize KORSUVA injection in dialysis patients with CKD-aP worldwide, excluding the U.S., Japan (Maruishi Pharma), and South Korea (CKD Pharma), and will promote KORSUVA injection, if approved, with VFMCRP in U.S. Fresenius Medical Care North America dialysis clinics under a profit share agreement. Additionally, CR845/difelikefalin has demonstrated efficacy in patients with moderate-to-severe pain, without inducing many of the undesirable side effects typically associated with currently available opioid pain therapeutics. Cara retains rights to all KORSUVA/ CR845 indications, excluding KORSUVA injection in dialysis patients with CKD-aP, worldwide, excluding Japan and South Korea.

The FDA has conditionally accepted KORSUVA™ as the trade name for difelikefalin injection. CR845/difelikefalin is an investigational drug product, and its safety and efficacy have not been fully evaluated by any regulatory authority.

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 future development of I.V. CR845 or meetings with regulators and the potential for I.V. CR845 to be a therapeutic option for perioperative pain management. 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, 2017, 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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