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Cara Therapeutics Announces Positive Top-Line Results From Phase 2a Trial of Oral CR845 in Chronic Pain Patients With Osteoarthritis of the Knee or Hip

- *Dose-related reduction observed in mean baseline pain score up to 34 percent after two weeks, with statistically significant reduction in mean rescue medication for top 5.0 mg dose*
- *All four tablet strengths observed to be safe and well tolerated*
- *Establishes therapeutic doses and dosing regimen for Phase 2b trial in 2016*
- *Conference call today at 8:30 a.m. ET*

SHELTON, Conn., Dec. 9, 2015 (GLOBE NEWSWIRE) -- Cara Therapeutics, Inc. (NASDAQ:CARA), a biotechnology company focused on developing and commercializing new chemical entities designed to alleviate pain and pruritus by selectively targeting kappa opioid receptors, today announced positive top-line results from a Phase 2a trial of an oral tablet formulation of the Company's peripherally selective kappa opioid agonist, CR845, in patients with osteoarthritis (OA) of the knee or hip. The results show:

- The mean joint pain score (NRS score) exhibited a dose-related reduction from baseline to the end of the two-week treatment period, ranging from -25 percent at the lowest (0.25 mg) tablet strength up to -34 percent for the highest (5.0 mg) tablet strength.
- 50 percent of the patients in the 5.0 mg dose group reported at least a 30 percent reduction in their pain score at the end of the treatment period.
- Integrated AUC analysis of the overall NRS score for the entire treatment period indicated a statistically significant reduction in the 5.0 mg dose group compared to the three lower doses used in the trial (Wilcoxon Rank Sum Test: p=0.02).
- The reduction in pain score in the 5.0 mg dose group was accompanied by a statistically significant reduction in mean rescue medication of approximately 80 percent (ANOVA: p= 0.02, for 5.0 mg vs lower dose groups).
- 59 percent of patients in the 5.0 mg dose group used no rescue medication in Week 2 of the trial.
- The effectiveness of the 5.0 mg dose was further supported by statistically significant, dose-related increases in the proportion of patients whose OA was "very much improved" or "much improved" as indicated by patient global assessment (Cochran-Mantel-Haenszel test, p=0.02, 2-sided).

An overall improvement in WOMAC scores was observed over time for all four tablet strengths, with the 5.0 mg dose group exhibiting a mean -38 percent improvement in WOMAC Index from baseline.

All tablet strengths were generally well tolerated with no drug-related SAEs. Dizziness (7 percent) and headache (6 percent) were the most common adverse events reported at the > 5 percent incidence level.

"These results are an important first step in establishing the applicability of an oral formulation of CR845 in treating chronic pain patients and expand the potential clinical utility of CR845 beyond our lead I.V. CR845 program in acute pain," said Derek Chalmers, Ph.D., D.Sc., President and Chief Executive Officer of Cara Therapeutics. "Based on these encouraging findings, we plan to conduct a larger double-blind, placebo-controlled Phase 2b trial in 2016."

The Phase 2a trial was a single-blind, randomized, multiple ascending dose trial designed to evaluate the safety, pharmacokinetics (PK) and effectiveness of oral CR845 tablets dosed over a two-week treatment period in OA patients experiencing moderate-to-severe pain, defined as > 4 on an 11-point Numerical Rating Scale (NRS) at baseline. Patients discontinued current pain medications five days prior to baseline measurements. Four tablet strengths (0.25 mg, 0.5 mg, 1.0 mg and 5.0 mg) were administered twice a day (b.i.d.) over a two-week treatment period in a total of 80 OA patients enrolled at five sites in the U.S. In addition to safety and PK observations, CR845's effectiveness was assessed by: change from baseline in joint pain using the Numeric Rating Scale (NRS), which was measured daily, change from baseline in the Western Ontario and McMaster Osteoarthritis Index (WOMAC), which was measured at the end of Weeks 1 and 2 of treatment, change from baseline in rescue medication use, measured daily, and Patient Global Assessment (PGA), which was measured on the last day of the study. Acetaminophen was the only allowable rescue medication.

PK analyses indicated dose-proportional exposure of CR845 after oral administration, with the 5.0 mg dose group exhibiting an approximately five-fold increased mean AUC value compared to the 1.0 mg dose group.

"The successful completion of this osteoarthritis trial is a key milestone on the path to establishing the potential clinical utility of

our oral CR845 formulation in the treatment of chronic inflammatory pain, for which NSAIDs and traditional mu opioids are frequently inadequate or unsafe," said Joseph Stauffer, D.O., M.B.A., Chief Medical Officer of Cara Therapeutics. "Although this Phase 2a study was designed primarily to confirm safety, tolerability and PK parameters in this challenging patient population, I'm very pleased that we obtained significant converging findings of dose-related effectiveness."

Conference Call

Cara management will host a conference call today at 8:30 a.m. ET to discuss the Oral CR845 OA trial results and next steps for the program.

To participate in the conference call, please dial (855) 445-2816 (domestic) or (484) 756-4300 (international) and refer to conference ID 3231404. 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 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 both pain intensity and opioid-related side effects. In more than 440 subjects dosed to date, I.V. CR845 was found to be safe and well tolerated, without incurring the dysphoric and psychotomimetic side effects that have been reported with centrally acting (CNS-active) kappa opioid receptor agonists. Cara initiated its Phase 3 Program of I.V. CR845 for acute pain with a first adaptive pivotal trial in laparoscopic abdominal surgery in 3Q'15.

About Tablet Formulation of Oral CR845

The oral tablet formulation of CR845 was synthesized utilizing the peptide formulation technology developed by Enteris Biopharma under a Manufacturing and Clinical Supply Agreement.

About Cara Therapeutics

Cara Therapeutics is a clinical-stage biotechnology company focused on developing and commercializing new chemical entities designed to alleviate pain and pruritus by selectively targeting kappa opioid receptors. Cara is developing a novel and proprietary class of product candidates that target the body's peripheral nervous system and have demonstrated 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 Oral CR845's potential to treat chronic pain patients and expand the potential clinical utility of CR845 beyond acute pain, the establishment of the clinical utility of Oral CR845 and the future clinical development of Oral CR845, including the expected timing for a Phase 2b clinical trial. 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 Therapeutics' filings with the Securities and Exchange Commission, including the "Risk Factors" section of the Company's Annual Report on Form 10-K for the year ended December 31, 2014, the Quarterly Report on Form 10-Q for the quarter ended September 30, 2015 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. Cara Therapeutics 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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