A Randomized, Double-Blind, Placebo-Controlled, Titration-to-Effect Study of Orally Administered CR845 in Patients with Osteoarthritis of the Hip or Knee

PROTOCOL NUMBER:	CR845-CLIN2002-PO
IND NUMBER:	113,440
DEVELOPMENT PHASE:	Phase 2
PROTOCOL TITLE:	A Randomized, Double-Blind, Placebo-Controlled, Titration-to-Effect Study of Orally Administered CR845 in Patients with Osteoarthritis of the Hip or Knee
PROTOCOL VERSION:	Version 3.0
DATE:	04 November 2016
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APPROVAL SIGNATURE

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Date
11/4/16

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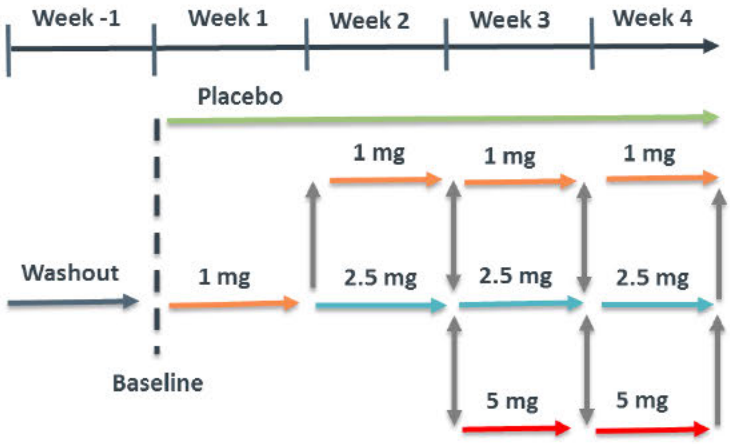
1. SYNOPSIS

PROTOCOL TITLE	A Randomized, Double-Blind, Placebo-Controlled, Titration-to-Effect Study of Orally Administered CR845 in Patients with Osteoarthritis of the Hip or Knee
PROTOCOL NUMBER	CR845-CLIN2002-PO
DEVELOPMENT PHASE	Phase 2
NAME OF ACTIVE INGREDIENT	CR845 - a selective *kappa*-opioid receptor agonist
ROUTE OF ADMINISTRATION	Oral (PO)
STUDY CENTERS	Approximately 40 sites in United States
STUDY DURATION (per patient)	Up to 80 days (2 weeks Screening; 8 weeks treatment; 1 week follow-up)
INDICATION	Treatment of chronic pain
STUDY POPULATION	Male and female patients (≥ 25 years of age) with moderate to severe pain (numeric rating scale [NRS] ≥ 5) associated with osteoarthritis (OA) of the hip or knee.
PLANNED NUMBER OF PATIENTS	The study is planned to enroll approximately 405 patients and will be randomized using a 2:1 (active: placebo) ratio. Randomization will be stratified based on a patient's primary OA joint (knee vs. hip). The sample size may be increased up to 480 total patients, depending on the results of a planned unblinded interim assessment to re-estimate the sample size. The interim assessment (IA) will occur when approximately 50% of the 405 patients have been randomized and have either completed the 8-week treatment period or have discontinued from treatment early.
INVESTIGATIONAL PRODUCT	CR845 and placebo tablets will be provided as enteric-coated tablets. All tablets are white in color with no markings and are identical in appearance, regardless of dose and treatment. CR845 tablets will be provided at doses of 1 mg, 2.5 mg and 5 mg.
TREATMENT REGIMEN	Dosing twice a day (BID) for a total of 8 weeks, with study medication recommended to be taken 2 hours before a meal or about 4 hours after a meal.
STUDY OBJECTIVES	**Primary Objective** • To characterize the analgesic efficacy of orally administered CR845 in patients with OA of the hip or knee

STUDY OBJECTIVES (continued)	**Secondary Objectives** • To compare the effect of treatment on patient function, pain and stiffness between CR845 and placebo-treated patients as measured by the Western Ontario and McMaster Osteoarthritis Index (WOMAC). • To compare the effect of treatment on the Patient Global Impression of Change (PGIC) between CR845- and placebo-treated patients. • To compare the use of analgesic rescue medications between CR845- and placebo-treated patients. • To characterize the safety and tolerability of titration-to-effect administration of oral CR845.
STUDY ENTRY CRITERIA	**Inclusion Criteria** A patient will be eligible for enrollment if the following criteria are met: 1. Voluntarily provides written informed consent to participate in the study prior to any study procedures. 2. Is able to speak, read, and communicate clearly in English or Spanish; is able to understand the study procedures. 3. Male or female ≥ 25 years of age. 4. Body mass index (BMI) ≤ 40 kg/m^2. 5. Has OA of the hip or knee according to American College of Rheumatology (ACR) criteria. 6. Reports an average pain intensity level ≥ 5 in the index joint at Screening on a 0-10 NRS scale. 7. Is either opioid-naïve (defined as taking < 10 mg a day of morphine equivalent 14 days prior to screening) or opioid-experienced. If receiving opioid analgesic medication for OA, patients must be on a stable dose ≤ 40 mg of morphine equivalents for 14 days prior to screening. 8. Willing to discontinue currently used pain medications beginning 5 days prior to the Baseline Visit and throughout the study. Acetaminophen use is allowed. (Section 8.8) 9. If female: a. Of childbearing potential – the patient must be willing to practice an acceptable form of birth control (defined as the use of an intrauterine device, a barrier method with spermicide, condoms, any form of hormonal contraceptives, or abstinence from sexual intercourse) for the duration of treatment and for at least 3 days following the last dose of study drug. b. Of non-childbearing potential – the patient must be surgically or biologically sterile (hysterectomy, bilateral oophorectomy, bilateral tubal ligation, or postmenopausal for at least 1 year).

STUDY ENTRY CRITERIA (continued)	10. If male, the patient must be surgically or biologically sterile. If not sterile, the patient must agree to use an acceptable form of birth control with a heterosexual partner (as described in inclusion criterion #9) or abstain from sexual relations during the treatment period and for 3 days following the last dose of study drug. 11. Is free of other physical, mental, or medical conditions that, in the opinion of the Investigator, would make study participation inadvisable. 12. Reports a daily pain intensity score in the index joint ≥ 5 (on a 0-10 NRS scale) during 4 or more of the last 7 days prior to randomization, with 2 consecutive days ≥ 5 occurring *just prior to randomization*. **Exclusion Criteria** A patient will be excluded from enrollment if the patient meets any of the following criteria: 1. Has had a joint replacement in the index joint. 2. Has received an intra-articular injection of corticosteroids or hyaluronic acid in any joint(s) within 3 months prior to the Screening Visit. 3. Has started a new medication for chronic illness within 30 days prior to the Screening Visit. 4. Is receiving opioid analgesic treatment for OA of the hip or knee at a dose > 40 mg of morphine equivalent. 5. Uses antipsychotics, antiepileptics, sedatives, hypnotics, or antianxiety agents, selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants with a dose change < 30 days prior to day 1 of the study. 6. Has a history or current diagnosis of substance dependence (except caffeine or nicotine) or alcohol abuse, according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). 7. Has a positive urine drug screen for drugs of abuse at Screening. 8. Has been diagnosed with a condition of hyperhidrosis (excessive sweating) or primary hypodipsia (a reduced sense of thirst). 9. Has a history (within 6 months) of clinically meaningful orthostatic changes in vital signs OR, at Screening, has a decrease in systolic blood pressure by > 20 mm Hg or a decrease in diastolic blood pressure by 10 mm Hg together with an increase in heart rate of > 30 beats per minute when transitioning from supine to standing measurements. 10. Has a medical condition (e.g., a cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine [adrenal hyperplasia], immunologic, dermatologic, neurologic, oncologic, or psychiatric) or a significant laboratory abnormality that, in the Investigator's opinion, would jeopardize the safety of the patient or is likely to confound the study measurements. 11. Has had any gastric bypass surgery, sleeve, or lap-band (for weight loss). 12. Has a corrected QT interval of > 450 msec in males, > 470 msec in females, or clinically significant abnormality on screening ECG.

STUDY ENTRY CRITERIA (continued)	13. Has a serum sodium level > 143 mmol/L at Screening or Baseline visit (i.e., Visit 2 prior to initiating study drug). 14. Has impaired renal function indicated by serum creatinine > 2 × the reference upper limit of normal (ULN). 15. Has a serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.5 × the reference ULN, or total bilirubin > 2 × the ULN at Screening. 16. Has, in the opinion of the Investigator, any clinical signs of dehydration or hypovolemia (e.g., symptomatic hypotension) or associated laboratory abnormalities (e.g., elevated hematocrit or elevated blood urea nitrogen [BUN] > 1.5 × the reference ULN) at Screening. 17. Has taken opioid or non-opioid pain medication (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs] such as naproxen or cyclooxygenase-2 inhibitors) within 5 days prior to study drug administration. Acetaminophen use is allowed. (Section 8.8) 18. Has received another investigational drug within 30 days prior to Baseline or has planned to participate in another clinical trial while enrolled in this study.
STUDY DESIGN	This is a multicenter, randomized, double-blind, placebo-controlled, titration-to-effect study of orally administered CR845 in patients with osteoarthritis of the hip or knee. The study schedule consists of a Screening Period (up to 14 days), a blinded 4- week Titration-to-Effect Period with weekly visits, a blinded 4-week Maintenance Treatment Period at the optimal dose level determined for each patient, and a 1-week Follow-up Period. Eligible patients will be randomized to receive either CR845 or placebo in a 2:1 ratio. Every patient will be started on a 1-mg dose of CR845 or matching placebo. During the post-randomization Titration-to-Effect period, the dose of study drug may be increased to 2.5 mg or 5 mg in a double-blind fashion. Patients may know their dose is being changed but will not know whether they were randomization to active study drug or placebo. Approximately 405 patients will be enrolled in this study. **Screening Period (Day -14 to Day 1):** Screening for this study must be conducted within 2 weeks of the Baseline visit. Screening (Visit 1) will consist of the following assessments: informed consent, review of enrollment criteria, medical history and demographics, prior medications, height, weight, physical examination, vital signs (supine and standing), 12-lead electrocardiogram (ECG), pregnancy test (if required), drug screening test, and clinical laboratory evaluations including serum sodium that must be $\leq$ 143mmol/L at screening. During this period, patients will be instructed on how to assess and accurately report their pain intensity.

STUDY DESIGN (continued)	Patients will keep a diary of their pain scores for the 7 days prior to their scheduled Baseline Visit. Final eligibility for study enrollment will be based upon diary pain scores for the 7 days prior to the Baseline visit. Only patients who report a daily pain intensity in the index joint ≥ 5 during 4 or more of the last 7 days prior to randomization, with 2 consecutive days ≥ 5 occurring *just prior to randomization*, and continue to satisfy all other inclusion/exclusion criteria will be randomized into the Titration-to-Effect period. **Titration-to-Effect Period (Days 1-28/Weeks 1-4):** CR845 is a highly charged peptide with limited bioavailability when administered orally. Based upon previous studies with oral CR845, a significant inter-patient variability in plasma concentrations of CR845 has been observed, which is likely due to differences in the absorption of CR845 from the gastrointestinal tract. It is presumed that patients who absorb CR845 well will not need higher doses to achieve an adequate analgesic response and patients who absorb the drug poorly will need to be titrated up to a higher dose to achieve a similar effect. The purpose of this Titration-to-Effect Period is to identify the optimal dose level of CR845 for each patient, based upon tolerability and efficacy, prior to the beginning of the 4-week Maintenance Treatment Period. Once patients enter into the Maintenance Treatment Period, the dose can no longer be changed. The double-blind, titration-to-effect period is 4 weeks in duration, with a clinic visit at the end of each 7-day period. All patients will be treated at each dose level for 1 week (7 days) prior to determining whether or not they should be moved to the next higher dose level. In a similar fashion, patients have the option after completing treatment Weeks 2, 3, or 4 to stay at their current dose level or return to their prior dose level if there are tolerability concerns.  On Day 1 of the study (Visit 2/Baseline), patients will be randomized to receive active treatment or placebo in a 2:1 ratio if serum sodium level is ≤ 143mmol/L. Randomization will be stratified according to primary OA joint (knee vs. hip). Patients who are randomized to active treatment will receive blinded 1 mg tablets of CR845 BID for 7 days. Patients who are randomized to placebo will receive blinded matching placebo tablets BID for 7 days.

STUDY DESIGN (continued)	At the end of this first week of treatment, patients will return to the clinical site for an evaluation (Visit 3/Day 8). This evaluation will consist of a review of the daily pain diary, the amount of rescue medication taken, any adverse events (AEs) or other safety event experienced during the prior week, and a serum sodium measurement. a. The decision by the clinical team to titrate up to the next dose level should be based primarily on tolerability. If the patient is tolerating the drug well with a limited analgesic response, he/she should be titrated up to the next dose level. b. If the patient has a good analgesic response after a single week of treatment (reduction from baseline in NRS pain score ≥ 2) and reports an average daily use of rescue medication < 1 g, then the patient should remain at the current dose, assuming the patient is tolerating the current dose. If the reduction from baseline in NRS pain scores is ≥ 2 and the patient desires to uptitrate, an increase in dose is allowed if deemed suitable by the Investigator based on clinical and tolerability assessments. If the patient has experienced adverse events during the first week of treatment that, in the opinion of the treating physician, may resolve spontaneously (e.g. headache, low back pain, upper respiratory infection [URI]), the clinical team (in conjunction with the patient) should determine if the patient should stay at the current dose level or be discontinued from the study. For the second week of treatment, patients whose dose was titrated from dose level 1 (1 mg) to the next dose level will receive either 2.5 mg tablets of CR845 or matching placebo BID for 7 days. Patients whose dose was maintained will continue to receive blinded 1 mg tablets of CR845 or matching placebo BID. At the end of this second week of treatment, patients will again return to the clinical site for an evaluation (Visit 4/Day 15). This evaluation will consist of a review of the daily pain diary, the amount of rescue medication taken, and any adverse events or other safety event experienced during that week.

STUDY DESIGN (continued)	The decision process at this visit is similar to the one followed at the end of Week 1, but with the additional option of down-titrating to the previous dose level: a. The decision by the clinical team to titrate up to the next dose level should be based primarily on tolerability. If the patient is tolerating the drug well with a limited analgesic response, he/she should be titrated up to the next dose level. b. If the patient has a good analgesic response after an additional week of treatment (reduction from baseline in NRS pain score ≥ 2) and reports an average daily use of rescue medication < 1 g, then the patient should remain at the current dose, assuming the patient is tolerating the current dose. If the reduction from baseline in NRS pain scores is ≥ 2 and the patient desires to uptitrate, an increase in dose is allowed if deemed suitable by the Investigator based on clinical and tolerability assessments. *c.* If the patient has experienced adverse events during the week of treatment that, in the opinion of the treating physician, may resolve spontaneously (e.g., headache, low back pain, URI), the clinical team (in conjunction with the patient) should determine if the patient should stay at the current dose level, *return to the previous dose level,* or be discontinued from the study. For the third week of treatment, patients whose dose was titrated from dose level 2 (2.5 mg) to dose level 3 (5.0 mg) will receive either 5.0 mg tablets of CR845 or matching placebo BID for 7 days. Patients whose dose was maintained will continue to receive blinded 2.5 mg tablets of CR845 or matching placebo BID. Patients whose dose was decreased will receive blinded 1.0 mg tablets of CR845 or matching placebo BID. At the end of the third week of treatment (Visit 5/Day 22), patients will again return to the clinical site for evaluation consisting of a review of the daily pain diary, the amount of rescue medication taken, any adverse events (AEs) or other safety event experienced during the prior week, and a serum sodium measurement. The decision to modify dosing or continue on the current dose will be made using the same criteria as defined above. Patients can only be up-titrated or down-titrated one dose level at a time. Therefore, at the end of Week 3, patients on dose level 3 (5.0 mg) can only be down-titrated to dose level 2 (2.5 mg). Patients receiving 2.5 mg of CR845 or matching placebo (dose level 2) can be up-titrated to dose level 3 (5 mg) or down-titrated to dose level 1 (1 mg). Finally, patients still receiving 1.0 mg of CR845 or matching placebo (dose level 1) can only be up-titrated to dose level 2 (2.5 mg).

STUDY DESIGN (continued)	Visit 5, occurring at the end of Week 3/Day 22, is the last visit where patients will have the option of titrating *up* to a higher dose (2.5 mg or 5 mg). At the end of Week 4 (Visit 6/Day 29), patients will again return to the clinical site for an evaluation consisting of a review of the daily pain diary, the amount of rescue medication taken, and any adverse events (AEs) or other safety event experienced during the prior week. At the end of Week 4, patients will only have the option of staying at their current dose or titrating down to a lower dose. During the Titration-to-Effect Period, patients are permitted to return to the clinical site for an unscheduled visit and have a dose decrease between 2 scheduled visits if deemed necessary. If at any time during the Titration-to-Effect Period, the patient's serum sodium level is > 150 mmol/L, dosing should be paused for patient assessment (i.e., retesting of sodium in approximately 1 hour after the patient is given a glass of water, and clinical evaluation). Based upon the outcome of the clinical evaluation by the clinical staff, the dosing of study medication will either be: a) continued or b) terminated. **Maintenance Treatment Period (Days 29-57/Weeks 4-8):** Following completion of the Titration-to-Effect Period at the end of Week 4 (Visit 6/Day 29), patients will begin 4 weeks of treatment at their optimal dose as long as their sodium level is ≤ 150 mmol/L. A full description of the activities to be conducted during the Maintenance Treatment Period can be found in Section 9.1.4. Two weeks of study medication and analgesic rescue medication will be dispensed to the patients at this visit. Patients will return to the clinic at the end of Week 6 (Visit 7/Day 43) to complete safety and efficacy assessments, including serum sodium, and study and rescue medication for the remaining 2 weeks of treatment will be dispensed at that time. Patients will return to the clinic for their final study visit at the end of Week 8 (Visit 8/Day 57). If at any time during the Maintenance Treatment Period, the patient's serum sodium level is > 150 mmol/L, dosing should be paused for patient assessment (i.e., retesting of sodium in approximately 1 hour after the patient is given a glass of water, and clinical evaluation). Based upon the outcome of the clinical evaluation by the clinical staff, the dosing of study medication will either be: a) continued or b) terminated. **Follow-Up Period (1-week posttreatment)**: Seven to 10 days after the last dose of study medication, patients will return to the study site for a follow-up safety evaluation.

ANALGESIC RESCUE MEDICATION	The use of rescue medication for the treatment of any pain (including but not limited to headache, menstrual cramps, or non-target joint pain) during the study will be discussed with the patients at the Screening Visit. Acetaminophen is the only allowable rescue medication for pain beginning from Day -5 until the end of the Maintenance Treatment Period. Starting at the Screening Visit Acetaminophen will be provided as 325-mg tablets and its use (number of tablets taken in the previous 24 hours) will be reported each evening in the patient diary. Acetaminophen should be taken as directed for pain, with a maximum allowable dose of up to 8 tablets per day (given 1-2 tablets every 4 to 6 hours as needed). However, the use of acetaminophen is not allowed for the 12 hours prior to a scheduled office visit until after the efficacy assessments have been completed, in order to minimize the confounding effects of rescue medication on these measures.
OUTCOME MEASURES	**Primary Efficacy Endpoint:** The primary efficacy endpoint for this study is the change from Baseline at Week 8/Day 57 with respect to the weekly mean of the daily pain intensity score at the index joint (measured using a NRS where 0 = no pain and 10 = worst possible pain). **Secondary Efficacy Endpoints:** The impact of treatment on pain, function, and stiffness will be assessed using the following secondary efficacy variables: • The change from baseline in the WOMAC total index score • The change from baseline in the WOMAC sub-scores of Pain, Stiffness, and Physical Function Other secondary endpoints include: • The Patient Global Impression of Change (PGIC) • The patient's pain response to treatment, defined as the percent improvement from baseline with respect to the weekly mean of the daily pain intensity score during the last week of the Maintenance Treatment Period • The amount of rescue medication (daily average number of tablets) used during the study and during the Maintenance Treatment period • The number and percentage of patients who withdraw from the study due to lack of analgesic efficacy **Safety Assessment**: Safety and tolerability of CR845 will be assessed by capturing a detailed medical and surgical history, ECGs, physical examinations, monitoring of treatment-emergent adverse events (TEAEs), vital signs, and laboratory evaluations.

STATISTICAL METHODS	**Analysis Populations**: The Safety and Full Analysis Populations (FAP) are both defined as the group of all randomized patients who received at least 1 dose of double-blind study drug. Following the intent-to-treat principle, patients in the FAP will be analyzed according to their randomized treatment, regardless of the actual treatment received. However, patients in the Safety Analysis Population will be analyzed according to their actual treatment. The Safety Population will be used to analyze all safety endpoints while the FAP will be used to analyze all efficacy endpoints. The Per-Protocol Population (PP) is defined as the subset of patients in the FAP who do not have any major protocol deviations that could affect the efficacy analyses. An analysis of the primary and secondary efficacy variables for the PP Population may be performed if more than 20% of the patients in the FAP are excluded. **Efficacy Analyses**: Every hypothesis test will be 2-sided and conducted at the 5% significance level. The primary efficacy endpoint is defined as the change from baseline at Week 8 with respect to the weekly mean of the daily 24-hour pain intensity score at the index joint. The baseline score will be calculated as the average of the 4 or more pain scores collected during the screening period that qualified the patient for randomization (inclusion criteria 12. The primary efficacy variable will be analyzed using a mixed effect model with repeated measures (MMRM). The model will contain treatment (placebo vs. CR845), treatment-by-week interaction as fixed effects, baseline value and OA joint (hip vs. knee) as covariates, and patient as a random effect. The treatment difference between CR845 (across all doses) and placebo at Week 8 will be estimated as the simple contrast in the treatment effect. The 2-sided 95% confidence interval, based on the difference in the least squares means between the 2 treatment groups (CR845 vs placebo) will be presented. The MMRM model will be implemented using SAS PROC MIXED. A restricted maximum likelihood (REML) method will be used . An appropriate covariance matrix will be used to model the within patient errors. The use of an unstructured covariance matrix structure as well as other structures, such as spatial patterns, that require fewer parameters (Toeplitz, autoregressive [1], or compound symmetry) will be examined. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom and adjust standard errors.

STATISTICAL METHODS (continued)	For the primary efficacy analysis, the treatment of missing data will be addressed using pattern mixture model methodology. Within each treatment, 4 data patterns will be defined as follows: • Pattern 1: will include patients who completed treatment on study drug. • Pattern 2: will include patients who discontinue treatment early due to adverse events. Missing data for these patients will be assumed to be similar to their pain score prior to the start of treatment. • Pattern 3: will include patients who discontinue treatment early due to lack of efficacy. Missing data for these patients will be assumed to be similar to their pain score prior to the start of treatment. • Pattern 4: will include patients who discontinue treatment early due to reasons other than adverse event or lack of efficacy. Missing data for these patients will be assumed to be similar to the scores for patients that are still in the study and randomized to the same treatment group. The pattern mixture model methodology will be implemented using SAS procedures MI and MIANALYZE. Sensitivity analyses will be conducted to assess the impact of the treatment of missing data on the study results. The analysis of the secondary efficacy variables is presented in Section 11 of the protocol. **Safety and Tolerability**: All safety data (AEs, clinical laboratory tests, and vital signs) will be listed by patient and summarized by group and time point as appropriate. Adverse events will be coded to preferred term (PT) and system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA). Interim Assessment An IA is planned when approximately 50% of the planned 405 patients have been randomized and have either completed the 8-week treatment period or have discontinued from treatment early. The IA will include a re-estimation of the final target sample size based on conditional power.
SAMPLE SIZE DETERMINATION	With 270 patients assigned to active treatment and 135 patients assigned to placebo (2:1 randomization), a total sample size of 405 patients will be sufficient to detect an effect size of 0.343 with > 90% power and a type 1 error rate of 5%.

2. TABLE OF CONTENTS

3. LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BID	twice a day
BMI	body mass index
BUN	blood urea nitrogen
CARA	Cara Therapeutics, Inc.
CFR	Code of Federal Regulations
CNS	central nervous system
CRF	case report form
CRO	contract research organization
CV	coefficient of variation
DIBD	development international birth date
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	electrocardiogram
eCRF	electronic case report form
FAP	Full Analysis population
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
IND	Investigational New Drug
IRB	Institutional Review Board
IV	intravenous
IVRS	interactive voice response system
IWRS	interactive web response system
LOCF	last observation carried forward
LOTE	lack of therapeutic efficacy
MCH	mean corpuscular hemoglobin

MCHC	mean corpuscular hemoglobin concentration
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MFMC	medium-fat, medium-calorie
MMRM	mixed effect model with repeated measures
NRS	numerical rating scale
NSAID	nonsteroidal anti-inflammatory drug
OA	osteoarthritis
PCP	phencyclidine
PGIC	Patient Global Impression of Change
PNS	peripheral nervous system
PO	oral (per os)
PP	Per-Protocol
PT	preferred term
RBC	red blood cell
REML	restricted maximum likelihood
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
SSRI	selective serotonin reuptake inhibitor
TEAE	treatment-emergent adverse event
THC	tetrahydrocannabinol
ULN	upper limit of normal
WBC	white blood cell
WHO-DD	World Health Organization Drug Dictionary
WOMAC	Western Ontario and McMaster Osteoarthritis Index

4. INTRODUCTION

4.1 Background and Rationale

CR845 is a selective kappa-opioid receptor agonist with a peripheral mechanism of action that is currently being developed by Cara Therapeutics, Inc. (CARA) as a novel therapeutic agent for the treatment of acute and chronic pain.

Opioid receptors are involved in the modulation of pain signals and consist of 3 subtypes: *mu, kappa*, and *delta*. These receptor subtypes are found in the central nervous system (CNS), in peripheral nervous system (PNS) tissues such as skin and viscera, and in the immune system.

Morphine, the most widely used opioid analgesic, acts primarily via activation of the *mu* opioid receptor located in the CNS and PNS. *Mu* opioid receptor activation is associated with a wide array of undesirable side effects, including sedation, respiratory depression, abuse liability, itching, and constipation. As a way to avoid these undesirable effects, CR845 was designed to activate *kappa* opioid receptors located in the PNS, which are known to modulate pain and inflammatory signals without producing the side effects reported after activation of *mu* opioid receptors.

CR845 is a potent and selective *kappa* receptor agonist with more than 30,000-fold selectivity over *mu* and *delta* opioid receptors and with no known activity at other non-opioid receptors, ion channels, or transporters. Its unique peptidic structure significantly differs from that of small molecule *kappa* opioid agonists developed to date, which, for the most part, are active within the CNS.

Due to its hydrophilic tetrapeptide structure, CR845 has limited membrane permeability by passive diffusion that limits its access to the CNS. Thus, the compound preferentially activates *kappa* opioid receptors located outside the CNS (e.g., in peripheral sensory nerves and ganglia).

Findings from nonclinical pharmacological studies in rodents have indicated that CR845 can decrease pain related to activation of nociceptors and/or nerve injury, decrease itch caused by different pruritogens, and reduce the production and release of pro-inflammatory mediators.

Intravenous (IV) and oral formulations of CR845 are being developed as treatments for postoperative and chronic pain, respectively, with the potential for reduced side effects and improved tolerability compared with currently available opioid medications. CR845 (IV) is also being evaluated for the treatment of uremic pruritus.

4.2 Clinical Experience

CR845 has been tested as oral capsules, oral tablets, and IV formulations.

To date, 818 subjects across 15 US studies and 2 Japanese studies have received CR845 treatment, 577 have been treated with an IV formulation and 241 have been treated with an oral formulation (capsules or tablets).

Subjects/patients were treated with single IV doses of CR845 ranging from 1 to 40 mcg/kg, or repeated IV dosing for up to a 48-hour period for a total dose up to 160 mcg/kg (i.e., 11 mg

over a 24-hour period). Studies using the IV formulation evaluated patients with postoperative pain (abdominal surgery and bunionectomy) and uremic pruritus.

Subjects/patients treated with the oral formulation were exposed to doses ranging from 0.25 mg to 10 mg in both fasted and fed conditions. Outpatients with OA of the hip or knee were treated in a small Phase 2a study evaluating doses up to 5 mg twice a day (BID).

Overall, CR845 has been shown to be safe and well tolerated when administered as both single and multiple IV or oral doses. A total of 650 patients/subjects have experienced treatment-emergent adverse events (TEAEs) have been reported in the program across active- and placebo-treated patients. There have been no deaths reported.

A cumulative total of 33 serious adverse events (SAEs) have been reported in patients exposed to CR845 in the both IV and PO studies from the time of the DIBD to March 2016, of which 9 SAEs were classified by the Investigators as being related to study drug. These events include hypernatremia/blood sodium increased (2 cases), sinus tachycardia (1 case), sedation (1 case), somnolence and drowsiness (2 cases), hypertension (1 case) and mental status changes (2 cases). All 9 of these events occurred in CR845-treated patients/subjects, with 7 of the 9 events occurring in the highest CR845 dose group (> 5mcg/kg IV). The other 2 SAEs were associated with lower doses of CR845 and occurred in the same hemodialysis patient.

While there is no apparent dose-relationship for CR845 in the reported adverse events (AEs) in any system organ class (SOC), it is clear that there are more AEs reported in each SOC for the highest CR845 dose groups (20 to 40 mcg/kg, IV). To mitigate the risks associated with the higher dose range, the highest dose to be evaluated in this study is 5 mg.

CR845 also produces a transient increase in urine output (on average, 0 to 12 hours after dosing) without a corresponding increase in electrolyte loss (i.e., increased excretion of free water only). This aquaretic activity, which is to be distinguished from the non–electrolyte-sparing action of diuretics, is a well-known pharmacological effect of *kappa* opioid agonists. This aquaretic effect may be related to reports of tachycardia and elevations in serum sodium that have been reported in CR845 clinical studies.

In contrast to the classical side effects reported with *mu* opioid agonists like morphine, respiratory depression related to the use of CR845 has not been reported. The relative abuse potential of CR845, compared to placebo or pentazocine (a schedule IV CNS-acting mixed *mu-kappa* partial agonist analgesic) has also been evaluated in recreational poly-drug users experienced with the use of opioids and hallucinogenic agents. In these patients/subjects, it was demonstrated that CR845 may present a low risk for abuse potential in humans in comparison to clinically used opioids. This observation is consistent with the absence of miosis after administration of CR845, a classical indicator of *mu* opioid CNS bioactivity, in contrast to the robust miosis observed in the same patients/subjects who are administered pentazocine.

4.2.1 Previous Studies with the Oral Formulation

Phase 1 Study in Healthy Volunteers: A phase 1 trial (CR845-CLIN1001-PO) testing enteric-coated capsules of CR845 (0.5 mg, 1 mg, 3 mg, or 10 mg) or matched placebo was completed December 2011 with 50 healthy volunteers and established the preliminary oral

bioavailability and safety parameters of CR845. Oral bioavailability was estimated to be approximately 16%, with maximal plasma concentration and overall exposure increasing in a linear fashion at ascending doses, and a time to maximal concentration of approximately 3 hours. Although variability was observed in systemic exposure (i.e., inter-individual bioavailability ranged from 1% to 43% with a coefficient of variation of 61.5%), the level of exposure at all doses was sufficient to activate peripheral *kappa* receptors, as indicated by an increase in serum prolactin, a known biomarker of *kappa* receptor activation (with prolactin levels comparable to those seen after administration of commonly used *mu* opioids). Oral CR845 was well tolerated and considered safe across all doses tested. There were no SAEs during the study, no severe AEs, no discontinuation of the study drug, and no subjects withdrew from the study due to AEs.

The most common TEAEs were increased orthostatic heart rate, abdominal discomfort and paresthesia. With the exception of abdominal discomfort, this TEAE profile is consistent with previous studies in humans with the IV formulation of CR845. Clinical laboratory results were generally stable throughout the study and no significant changes in electrocardiogram (ECG) measurements were reported.

The consumption of a high-fat meal decreased the exposure of CR845 and delayed its oral absorption relative to fasting subjects (t_{max} ~ 12 hours) and mean estimate of oral bioavailability of 3%), suggesting that this formulation should not be taken at the time of a high-fat meal.

Phase 2 Study in Patients with Osteoarthritis: A Phase 2a multiple ascending-dose pilot study (CR845-CLIN2001-PO) in patients with osteoarthritis (OA) of the hip and knee was completed in October 2015. Four different doses of CR845 were evaluated over a 2-week treatment period in a single-blinded study (0.25-, 0.5-, 1- and 5-mg tablets BID; n=20 per treatment group).

Safety and Tolerability: CR845 was well tolerated in the first 3 treatment groups (0.25- 0.5- and 1-mg tablets BID). An increase in AEs was noted in the 5-mg dose group (4 patients discontinued secondary to dizziness). In addition, although no patients were symptomatic, there was a dose-related increase in the number of slightly elevated serum sodium levels observed during the study. The majority of cases were between 146 to 147 mmol/L (normal range: 135 to 145 mmol/L). No patients exceeded a serum sodium level of 150 mmol/L.

Efficacy: All treatment groups showed a continued improvement over time in numerical rating scale (NRS) pain scores (index joint) with a percent improvement on Day 15 ranging from 25 to 31% (last observation carried forward [LOCF]) and 25 to 26% (mixed imputation).

4.3 Summary of Potential Risks and Benefits

CR845 is a novel analgesic medication that could provide benefit to patients with acute or chronic pain.

Treatment with CR845 has not generally been associated with the AEs often experienced with mu-opioid receptor agonists such as constipation, nausea and vomiting, respiratory depression,

itching, cognitive impairment or abuse liability, nor does it appear to have the gastrointestinal or cardiovascular risks associated with nonsteroidal anti-inflammatory drug (NSAID) use.

The incidences of nausea and vomiting observed in the Phase 2a OA study were 6% and 2% respectively, lower than rates reported for mu-opioid receptor agonists.

A fully detailed summary of the potential risks and benefits of CR845 is provided in the Investigator's Brochure (IB).[1] The Investigator must become familiar with all sections of the current IB for CR845 before the start of the study.

5. STUDY OBJECTIVES

5.1 Primary Objective

- To characterize the analgesic efficacy of orally administered CR845 in patients with OA of the hip or knee.

5.2 Secondary Objectives

- To compare the treatment effect on patient function, pain and stiffness between CR845- and placebo-treated patients as measured by the Western Ontario and McMaster Osteoarthritis Index (WOMAC).
- To compare the treatment effect on Patient Global Impression of Change between CR845- and placebo-treated patients.
- To compare the use of analgesic rescue medications between CR845- and placebo-treated patients.
- To characterize the safety and tolerability of titration-to-effect administration of oral CR845.

6. INVESTIGATIONAL PLAN

6.1 Study Design

This is a multicenter, randomized, double-blind, placebo-controlled, titration-to-effect study of orally administered CR845 in patients with OA of the hip or knee.

Eligible patients will be randomized to receive either CR845 (1 mg-, 2.5 mg- or 5-mg tablets) or placebo in a 2:1 ratio. Approximately 405 patients will be enrolled in this study.

The study schedule consists of a Screening Period (up to 14 days), a blinded 4-week Titration-to-Effect Period with weekly visits, a blinded 4-week Maintenance Treatment Period at the optimal dose level determined for each patient, and a Follow-Up Period.

Screening Period (Visit 1/Day -14 to Day -1): Screening for this study must be conducted within 2 weeks of the Baseline visit.

Screening will consist of the following assessments: informed consent, review of enrollment criteria, medical history and demographics, prior medications, height, weight, physical examination, vital signs (supine and standing), 12-lead ECG, pregnancy test (if required), drug screening test, and clinical laboratory evaluations including serum sodium level that must be ≤ 143 mmol/L at screening. During this period, patients will also be instructed on how to assess and accurately report their pain intensity.

Patients will keep a diary of their pain scores for the 7 days prior to their scheduled Baseline Visit. Final eligibility for study enrollment will be based upon diary pain scores for the 7 days prior to the Baseline visit. Only patients who report a daily pain intensity in the index joint ≥ 5 during 4 or more of the last 7 days prior to randomization, with 2 consecutive days ≥ 5 occurring *just prior to randomization*, and continue to satisfy all other inclusion/exclusion criteria (Section 7.1 and Section 7.2) will be randomized into the Titration-to-Effect period.

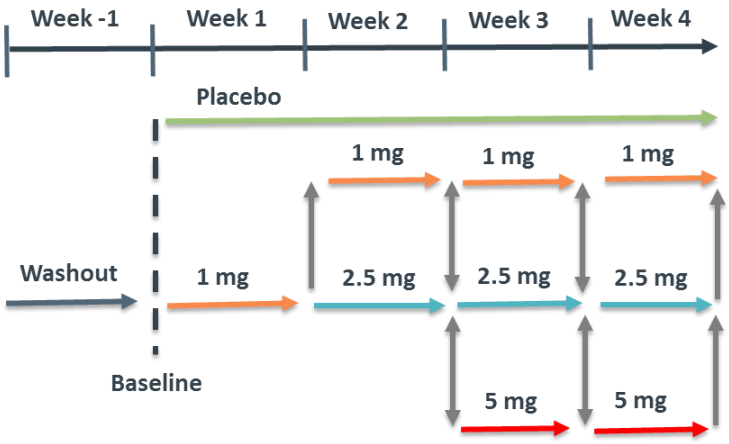
Titration-to-Effect Period (Days 1-28/Weeks 1-4):

CR845 is a highly charged peptide with limited bioavailability when administered orally. Based upon previous studies with oral CR845, a significant inter-patient variability in plasma concentrations of CR845 has been observed that is likely due to differences in the absorption of CR845 from the gastrointestinal tract. It is presumed that patients who absorb CR845 well will not need higher doses to achieve an adequate analgesic response and patients who absorb the drug poorly will need to be titrated up to a higher dose to achieve a similar effect.

The purpose of this Titration-to-Effect Period is to identify the optimal dose level of CR845 for each patient, based upon tolerability and efficacy, prior to the beginning of the 4-week Maintenance Treatment Period. Once patients enter into the Maintenance Treatment Period, the dose level can no longer be changed.

The Titration-to-Effect Period is 4 weeks in duration, with a clinic visit at the end of each 7-day period. Patients will be treated at each dose level for 1 week (7 days) prior to determining whether or not they should be moved to the next higher/lower dose level or stay at their current dose level (see Figure 1).

Figure 1: Titration-to-Effect Scheme



On Day 1 of the study (Visit 2/Baseline), patients will be randomized to receive active treatment or placebo in a 2:1 ratio if serum sodium level is ≤ 143 mmol/L. Randomization will be stratified according to primary OA joint (knee versus hip). Patients who are randomized to active treatment will receive blinded 1-mg tablets of CR845 BID for 7 days. Patients who are randomized to placebo will receive blinded matching placebo tablets BID for 7 days.

At the end of this first week of treatment, patients will return to the clinical site for an evaluation (Visit 3/Day 8). This evaluation will consist of a review of the daily pain diary, the amount of rescue medication taken, any adverse events (AEs) or other safety event experienced during the prior week, and a serum sodium measurement.

a. The decision by the clinical team to titrate up to the next dose level should be based primarily on tolerability. If the patient is tolerating the drug well with a limited analgesic response, he/she should be titrated up to the next dose level.
b. If the patient has a good analgesic response after a single week of treatment (reduction from baseline in NRS pain score > 2) and reports an average daily use of rescue medication < 1 g, then the patient should remain at the current dose, assuming the patient is tolerating the current dose. If the reduction from baseline in NRS pain scores is ≥ 2 and the patient desires to uptitrate, an increase in dose is allowed if deemed suitable by the Investigator based on clinical and tolerability assessments.
c. If the patient has experienced AEs during the first week of treatment that, in the opinion of the treating physician, may resolve spontaneously (e.g. headache, low back pain, upper respiratory infection, the clinical team (in conjunction with the patient) should determine if the patient should stay at the current dose level or be discontinued from the study.

For the second week of treatment, patients whose dose was titrated from dose level 1 (1 mg) to the next dose level will receive either 2.5-mg tablets of CR845 or matching placebo BID for 7 days. Patients whose dose was maintained will continue to receive blinded 1-mg tablets of CR845 or matching placebo BID.

At the end of this second week of treatment, patients will again return to the clinical site for an evaluation (Visit 4/Day 15). This evaluation will consist of a review of the daily pain diary, the amount of rescue medication taken, and any adverse events or other safety event experienced during that week.

The decision process at this visit is similar to the one followed at the end of Week 1, but with the additional option of down-titrating to the previous dose level:

a. The decision by the clinical team to titrate up to the next dose level should be based primarily on tolerability. If the patient is tolerating the drug well with a limited analgesic response, he/she should be titrated up to the next dose level.

b. If the patient has a good analgesic response after an additional week of treatment (reduction from baseline in NRS pain score ≥ 2) and reports an average daily use of rescue medication < 1 g, then the patient should remain at the current dose, assuming the patient is tolerating the current dose. If the reduction from baseline in NRS pain scores is ≥ 2 and the patient desires to uptitrate, an increase in dose is allowed if deemed suitable by the Investigator based on clinical and tolerability assessments.

c. If the patient has experienced AEs during the week of treatment that, in the opinion of the treating physician, may resolve spontaneously (e.g., headache, low back pain, upper respiratory infection), the clinical team (in conjunction with the patient) should determine if the patient should stay at the current dose level, return to the previous dose level, or be discontinued from the study.

For the third week of treatment, patients whose dose was titrated from dose level 2 (2.5 mg) to dose level 3 (5.0 mg) will receive either 5.0-mg tablets of CR845 or matching placebo BID for 7 days. Patients whose dose was maintained will continue to receive blinded 2.5-mg tablets of CR845 or matching placebo BID. Patients whose dose was decreased will receive blinded 1.0-mg tablets of CR845 or matching placebo BID.

At the end of the third week of treatment (Visit 5/Day 22), patients will again return to the clinical site for evaluation consisting of a review of the daily pain diary, the amount of rescue medication taken, any AEs or other safety event experienced during the prior week, and a serum sodium measurement. The decision to modify dosing or to continue on the current dose will be made using the same criteria as defined above. Patients can only be up-titrated or down-titrated one dose level at a time. Therefore, at the end of Week 3, patients on dose level 3 (5.0 mg) can only be down-titrated to dose level 2 (2.5 mg). Patients receiving 2.5 mg of CR845 or matching placebo (dose level 2) can be up-titrated to dose level 3 (5 mg) or down-titrated to dose level 1 (1 mg). Finally, patients still receiving 1.0 mg of CR845 or matching placebo (dose level 1) can only be up-titrated to dose level 2 (2.5 mg).

Visit 5, occurring at the end of Week 3/Day 22, is the last visit where patients will have the option of titrating *up* to a higher dose (2.5 mg or 5 mg).

At the end of Week 4 (Visit 6/Day 29), patients will again return to the clinical site for an evaluation consisting of a review of the daily pain diary, the amount of rescue medication taken, and any adverse events (AEs) or other safety event experienced during the prior week.

At the end of Week 4, patients will only have the option of staying at their current dose or titrating down to a lower dose.

During the Titration-to-Effect Period, patients are permitted to return to the clinical site for an unscheduled visit and have a dose decrease between 2 scheduled visits if deemed necessary.

If at any time during the Titration-to-Effect Period, the patient's serum sodium level is > 150 mmol/L, dosing should be paused for patient assessment (i.e., retesting of sodium in approximately 1 hour after the patient is given a glass of water, and clinical evaluation). Based upon the outcome of the clinical evaluation of the patient by the clinical staff, the dosing of study medication will either be: a) continued or b) terminated.

Maintenance Treatment Period (Days 29-57/Weeks 4-8):

Following completion of the Titration-to-Effect Period at the end of Week 4 (Visit 6/Day 29), patients will begin 4 weeks of treatment at their optimal dose as long as their sodium level is ≤ 150 mmol/L. A full description of the activities to be conducted during the Maintenance Treatment Period can be found in Section 9.1.4.

Two weeks of study medication and analgesic rescue medication will be dispensed to the patients at this visit. Patients will return to the clinic at the end of Week 6 (Visit 7/Day 43) to complete safety and efficacy assessments, including serum sodium, and study and rescue medication for the remaining 2 weeks of treatment will be dispensed at that time. Patients will return to the clinic for their final study visit at the end of Week 8 (Visit 8/Day 57).

If at any time during the Maintenance Treatment Period, the patient's serum sodium level is > 150 mmol/L, dosing should be paused for patient assessment (i.e., retesting of sodium in approximately 1 hour after the patient is given a glass of water and clinical evaluation). Based upon the outcome of the clinical evaluation of the patient by the clinical staff, the dosing of study medication will either be: a) continued or b) terminated.

Follow-Up Period (1-week post treatment):

Seven to 10 days after the last dose of study medication, patients will return to the study site for a follow-up safety evaluation.

6.2 Number of Patients and Sites

The study is planned to enroll approximately 405 patients and will be randomized using a 2:1 (active: placebo) ratio.

The study will be conducted at up to 40 sites in the United States.

6.3 Duration of Treatment

The duration of treatment in this study is 8 weeks (56 days). The total duration of the study (including the Screening Period and the Follow-Up Period) is a maximum of 12 weeks (84 days).

6.4 Stopping Rules

Elevations of serum sodium have been associated with the PO administration of CR845. Based upon this potential risk, dosing for an individual patient should be paused and the patient should be evaluated if serum sodium levels are observed to be > 150 mmol/L at any time during the study. The patient should be assessed (i.e., retesting of sodium in approximately 1 hour after the patient is given a glass of water) and clinically evaluated. Based upon the outcome of the clinical evaluation of the patient by the clinical staff, the dosing of study medication will either be: a) continued or b) terminated.

6.5 Safety Monitoring Team (SMT)

A safety monitoring team at Cara Therapeutics, Inc. will meet periodically to review all blinded safety data as the study progresses. These data will include, but are not limited to:

- Treatment-emergent AEs that result in an early study withdrawal
- Serious AEs
- Serum sodium levels

Appropriate action will be taken based upon this review. All events will be managed and reported in compliance with all applicable regulations and included in the final clinical study report.

7. PATIENT POPULATION

The study population will consist of male and female patients aged ≥ 25 years with moderate to severe pain associated with OA of the hip or knee. All inclusion/exclusion criteria must be met before the patient is enrolled.

A Screening log of potential study candidates and an enrollment log of patients must be maintained at each study site.

No medical waivers for enrollment will be provided during this study.

7.1 Inclusion Criteria

A patient will be eligible for enrollment if the following criteria are met:

1. Voluntarily provides written informed consent to participate in the study prior to any study procedures.
2. Is able to speak, read, and communicate clearly in English or Spanish; is able to understand the study procedures.
3. Male or female ≥ 25 years of age.
4. Body mass index (BMI) ≤ 40 kg/m^2.
5. Has OA of the hip or knee according to American College of Rheumatology (ACR) criteria.
6. Reports an average pain intensity level ≥ 5 in the index joint at Screening on a 0-10 NRS scale.
7. Is either opioid-naïve (defined as taking < 10 mg a day of morphine equivalent 14 days prior to screening) or opioid-experienced. If receiving opioid analgesic medication for OA, patients must be on a stable dose ≤ 40 mg of morphine equivalents for 14 days prior to screening.
8. Willing to discontinue all currently used pain medication beginning 5 days prior to the Baseline Visit and throughout the study. Acetaminophen use is allowed. (Section 8.8).
9. If female:
    a. Of childbearing potential – the patient must be willing to practice an acceptable form of birth control (defined as the use of an intrauterine device, a barrier method with spermicide, condoms, any form of hormonal contraceptives, or abstinence from sexual intercourse) for the duration of treatment and for at least 3 days following the last dose of study drug.
    b. Of non-childbearing potential – the patient must be surgically or biologically sterile (hysterectomy, bilateral oophorectomy, bilateral tubal ligation, or postmenopausal for at least 1 year).
10. If male, the patient must be surgically or biologically sterile. If not sterile, the patient must agree to use an acceptable form of birth control with a heterosexual partner (as described in inclusion criterion #9) or abstain from sexual relations during the treatment period and for 3 days following the last dose of study drug.

11. Is free of other physical, mental, or medical conditions that, in the opinion of the Investigator, would make study participation inadvisable.
12. Reports a daily pain intensity score in the index joint ≥ 5 (on a 0-10 NRS scale) during 4 or more of the last 7 days prior to randomization, with 2 consecutive days ≥ 5 occurring just prior to randomization.

7.2 Exclusion Criteria

A patient will be excluded from enrollment if the patient meets any of the following criteria:

1. Has had a joint replacement in the index joint.
2. Has received an intra-articular injection of corticosteroids or hyaluronic acid in any joint(s) within 3 months prior to the Screening Visit.
3. Has started a new medication for chronic illness within 30 days prior to the Screening Visit.
4. Is receiving opioid analgesic treatment for OA of the hip or knee at a dose > 40 mg of morphine equivalent.
5. Uses antipsychotics, antiepileptics, sedatives, hypnotics, or antianxiety agents, selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants with a dose change < 30 days prior to day 1 of the study.
6. Has a history or current diagnosis of substance dependence (except caffeine or nicotine) or alcohol abuse, according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).
7. Has a positive urine drug screen for drugs of abuse at Screening.
8. Has been diagnosed with a condition of hyperhidrosis (excessive sweating) or primary hypodipsia (a reduced sense of thirst).
9. Has a history (within 6 months) of clinically meaningful orthostatic changes in vital signs OR, at Screening, has a decrease in systolic blood pressure by > 20 mm Hg or a decrease in diastolic blood pressure by 10 mm Hg together with an increase in heart rate of > 30 beats per minute when transitioning from supine to standing measurements.
10. Has a medical condition (e.g., a cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine [adrenal hyperplasia], immunologic, dermatologic, neurologic, oncologic, or psychiatric) or a significant laboratory abnormality that, in the Investigator's opinion, would jeopardize the safety of the patient or is likely to confound the study measurements.
11. Has had any gastric bypass surgery, sleeve, or lap-band (for weight loss).
12. Has a corrected QT interval > 450 msec in males, or > 470 msec in females or clinically significant abnormality on screening ECG.
13. Has a serum sodium level > 143 mmol/L at Screening or Baseline (i.e., Visit 2 prior to initiating study drug).

14. Has impaired renal function indicated by serum creatinine > 2 × the reference upper limit of normal (ULN).
15. Has a serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.5 × the reference ULN, or total bilirubin > 2 × the ULN at Screening.
16. Has, in the opinion of the Investigator, any clinical signs of dehydration or hypovolemia (e.g., symptomatic hypotension) or associated laboratory abnormalities (e.g., elevated hematocrit or elevated blood urea nitrogen [BUN] > 1.5 × the reference ULN) at Screening.
17. Has taken opioid or non-opioid pain medication (e.g., NSAIDs such as naproxen or cyclo-oxygenase-2 inhibitors) within 5 days prior to study drug administration. Acetaminophen use is allowed. (Section 8.8)
18. Has received another investigational drug within 30 days prior to Baseline or has planned to participate in another clinical trial while enrolled in this study.

7.3 Clinical Surveillance Team (CST) Eligibility Assessment

The Clinical Surveillance Team (CST) is a division of INC Research CNS Clinical Development. The CST eligibility assessment will be reviewed by the CST, along with the Sponsor, based on protocol-specified inclusion and exclusion criteria to promote appropriate patient enrollment and data quality. Sites will complete the CST Eligibility Packet at screening and submit the data to the CST for review. This submission and review should be completed as soon as possible after screening and prior to baseline. Decisions regarding inclusion of patients and assessment of patient safety throughout the trial primarily remain at the discretion of the Investigator; however, the Medical Monitor or Sponsor may request exclusion or discontinuation of a patient based on entry criteria or patient safety.

7.4 Premature Patient Withdrawal

All patients will be advised at the time of informed consent that they are free to withdraw from participation in this study at any time, for any reason, and without prejudice. Every reasonable attempt should be made by the Investigator to keep patients in the study; however, patients must be withdrawn from the study if they withdraw their consent to participate. Investigators must attempt to contact patients who fail to attend scheduled visits by telephone or other means to exclude the possibility of an AE being the cause of withdrawal. Should this be the cause, the AE must be documented, reported, and followed as described in Section 10.

The Sponsor reserves the right to request the withdrawal of a patient due to protocol violations or other reasons.

The Investigator also has the right to withdraw patients from the study at any time for lack of therapeutic effect that is intolerable or otherwise unacceptable to the patient, for intolerable or unacceptable AEs, noncompliance with study procedures, administrative reasons, or in the Investigator's opinion, to protect the patient's best interest.

If a patient is withdrawn before completing the study, the reason for the withdrawal and the date of study discontinuation will be recorded on the appropriate electronic case report form (eCRF). Whenever possible and reasonable, the evaluations that were to be conducted at the completion of the study should be performed at the time of premature discontinuation.

7.5 Patient Replacement Criteria

Withdrawn patients who have received study drug will not be replaced. If a substantial number of patients withdraw from the study, then the Sponsor will evaluate the need for developing replacement criteria.

Enrolled patients withdrawn from the study may not re-enter. The patient number for a withdrawn patient will not be reassigned to another patient.

7.6 Counseling Women of Childbearing Potential

All women are considered to be of childbearing potential unless they are surgically or biologically sterile (e.g., hysterectomy, bilateral oophorectomy, bilateral tubal ligation or postmenopausal for at least 1 year).

All women of childbearing potential should be counseled on the need to practice adequate birth control during the use of study drug and on the importance of avoiding pregnancy.

Medically acceptable methods of birth control include any form of a hormonal contraceptive, a barrier method with spermicide, condoms, intrauterine device, vasectomized partner (vasectomy 6 months prior to Screening), or abstinence from heterosexual intercourse starting after informed consent, for the duration of the study, and continuing for 3 days after the last dose of study drug. Women should be told to contact the Investigator or his/her staff immediately if pregnancy is suspected.

8. STUDY TREATMENTS

8.1 Investigational Product

CR845 will be provided as enteric-coated tablets at doses of 1 mg, 2.5 mg and 5 mg with matching placebo tablets. All tablets are white in color with no markings and are identical in appearance, regardless of dose.

Study medication should be stored refrigerated but may be brought to room temperature prior to dosing. CR845 tablets can be maintained at room temperature for several hours without any impact on drug stability. This would include the time required for patients to transport the tablets to and from home for clinic visits.

The tablets are manufactured and packaged in high-density polyethylene bottles of 15 tablets by Enteris BioPharma (Boonton, NJ). Labeling of CR845 tablets will be conducted at Sherpa Clinical Packaging (San Diego CA).

8.1.1 Labeling

Each bottle of CR845 tablets will be labeled and placed into secondary packaging.

The study drug will be provided in identical kits and numbered so that treatment cannot be identified.

Each bottle of tablets will be labeled to include the following information:

- Study Protocol number
- Patient ID Number
- Temperature storage instructions
- Retest date
- Name and location of Sponsor
- The following statements:
    i. Administration according to study protocol
    ii. Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use

8.2 Dispensing and Storage

The study medication is to be used exclusively in the clinical study according to the instructions of this protocol. The Investigator is responsible for dispensing the study medication according to the dosage scheme and for ensuring proper storage of the study medication.

The Investigator must confirm receipt of the study medication with his/her signature. A copy of this receipt must be kept by the Investigator and another copy will be stored at CARA and/or INC Research. Until the medication is dispensed to the patients, it must be stored at 2° to 8°C in a securely locked area that is not generally accessible.

The key to the storage area is to be kept by the Investigator or designee responsible for the study medication. The storage area will be accessible only to those persons authorized by the Investigator to dispense the study medication.

8.3 Method of Assigning Patients to Treatment Groups

This is a multicenter, randomized, double-blind, placebo-controlled, titration-to-effect study of orally administered CR845 in patients with osteoarthritis of the hip or knee.

Eligible patients will be randomized to receive either CR845 or placebo in a 2:1 ratio, and will be stratified according to their primary joint affected by OA (knee vs. hip). Randomization will be performed using an Interactive Web Response System (IWRS). Approximately 405 patients will be enrolled in this study.

Because of the known titration scheme during the Titration-to-Effect Period, the clinical staff may be aware of the dose being administered, but all attempts should be made to keep the patients blinded as to the study dose being administered during both titration and treatment.

8.4 Emergency Unblinding

Emergency unblinding (via IWRS) of treatment assignment for a patient may be necessary due to a medical emergency, such as an SAE that is unexpected and for which a causal relationship to study drug cannot be ruled out or any other significant medical event (e.g., pregnancy).

If emergency unblinding is required for a medical emergency:

- Only the Investigator will make the decision to unblind the treatment assignment.
- Only the patient with the medical emergency will be unblinded.

The Investigator should notify the INC Medical Director and/or designee prior to breaking the blind, whenever possible. In all cases, the INC Medical Director and/or designee must be notified within 24 hours of the blind being broken.

8.5 Selection of Doses in the Study

The doses of CR845 to be evaluated in this study were selected based upon the results of the multiple-dose Phase 1 study of oral tablets in healthy volunteers (CLIN1002-PO) and a Phase 2a study in patients with OA of the hip or knee.

8.6 Selection of Timing of Dose for Each Patient

In the Phase 1 study of oral tablets in healthy volunteers (CLIN1002-PO), the effect of meal timing on the oral absorption of CR845 tablets was evaluated by dosing the drug at either fasted conditions or at 1 hour before, 2 hours before, or 2 hours after a medium-fat, medium-calorie (MFMC) meal.

In general, the mean concentration-time profiles for tablets administered 2 hours prior to meals were similar to the profiles observed following fasted conditions. However, when tablets were administered 1 hour prior or 2 hours after a meal, the overall plasma exposure of CR845

was reduced by ~ 50%. These data suggest that the optimal time for the oral dosing of CR845 is at least 2 hours prior to meals.

8.7 Dosing Regimen

Study medication will be taken BID. It is recommended that the medication be taken 2 hours before a meal or about 4 hours after a meal. The first dose should be taken at mid-morning (9:30-10 am) assuming breakfast is between 6 and 7 am and lunch is after 12 pm and the second dose should be taken just before going to bed at night, 4 hours post the last meal.

Study medication should be taken with a full glass of water (250 mL).

8.8 Analgesic Rescue Medication

The use of rescue medication for the treatment of any pain (including but not limited to headache, menstrual cramps, or non-target joint pain) during the study will be discussed with the patients at the Screening Visit. Acetaminophen is the only allowable rescue medication for pain beginning from Day -5 until the end of the Maintenance Treatment Period.

Acetaminophen will be provided as 325-mg tablets and its use (number of tablets taken in the previous 24 hours) will be reported each evening in the patient diary. Drug accountability will also be conducted at each clinic visit starting at the Screening Visit and continuing through the End-of-Study Visit (Visit 8).

Acetaminophen should be taken as directed for pain, with a maximum allowable dose of 8 tablets per day (given 1 to 2 tablets every 4 to 6 hours as needed). However, the use of acetaminophen is not allowed *for the 12 hours prior to a scheduled office visit* until after the efficacy assessments have been completed, in order to minimize the confounding effects of rescue medication on these measures.

8.9 Drug Accountability

The Investigator must maintain adequate records showing the receipt, dispensing, return, or other disposition of the study medication including the date, quantity, batch or code number, and identification of patients (patient number and initials) who received the study medication. The Investigator will not supply the study medication to any person except those named as sub-investigators on the Form Food and Drug Administration (FDA) 1572, designated study personnel, and patients in this study. The Investigator will not dispense the study medication from any study sites other than those listed on the Form FDA 1572. The study medication may not be relabeled or reassigned for use by other patients. If any of the study medication is not dispensed or is lost, stolen, spilled, unusable, or received in a damaged container, this information must be documented and reported to CARA and appropriate regulatory agencies, as required.

Upon completion of the study, the study medication (partly used, unused, and empty bottles) must be left in the original packaging and destroyed at the site or returned to the Sponsor or designee for destruction.

8.10 Treatment Compliance

All patients will receive the first dose of study medication at the study site under the surveillance of appropriate study personnel. The dosing time will be recorded in the patient's eCRF.

A visit window of plus or minus one day will be allowed.

Treatment compliance with study medication regimens will be assessed by study personnel via tablet counts of returned medication and by questioning the patient, if necessary, at every posttreatment visit.

Patients will be considered noncompliant if they miss more than one dose during the Titration-to-Effect period and will be discontinued from the study.

Patients will be considered noncompliant if their overall study drug use is not within 80% to 110% (inclusive) of the expected drug use during the Maintenance Treatment period. A patient who is not compliant (took < 80% or > 110% of study medication) will be discontinued from the study.

In addition, for each 7-day administration period, patients will be asked to record their daily intake of study medication on a diary card. These diaries will be reviewed by study personnel at each visit and will be collected as source documents. Information from the patient diary will be transcribed onto the appropriate eCRF pages for documentation of patient compliance with study medication.

8.11 Prior and Concomitant Medications

Prior medications are defined as those that the patient has taken at any time during the 30 days prior to the Screening Visit up until administration of the first dose of study drug. Concomitant medications are defined as medications that are taken at any time from after the administration of the first dose of study drug through the end of the study.

All prior and concomitant medications, including over-the-counter medications, used by patients during this study, are to be recorded in the appropriate source documents at each study visit, and recorded on the appropriate page of the eCRF.

Patients taking antianxiety agents, selective serotonin reuptake inhibitors (SSRIs), or other medications to treat a chronic condition (e.g., hypothyroidism, hypertension) for more than 1 month prior to the study and who expect to remain on stable doses throughout the duration of the study will be eligible to participate if their conditions are well controlled in the opinion of the Investigator.

Low-dose aspirin (acetylsalicylic acid), defined as up to 81 mg daily, taken for cardio-protection is allowed.

8.12 Prohibited Medications

Patients who meet the initial eligibility criteria at the Screening Visit will be asked to discontinue their current NSAID and opioid analgesic medications beginning 5 days prior to randomization (Day -5) and continuing for the duration of the study (through Day 57).

Intra-articular injections of either corticosteroids or hyaluronic acid in any joint within 3 months prior to Screening and for the duration of the study are prohibited.

9. STUDY PROCEDURES

Patients will provide written informed consent before any study-related procedures are initiated.

For the timing of assessments and procedures throughout the study, refer to the schedule of events (Section 15). Throughout the study, every reasonable effort should be made by study personnel to follow the timing of assessments and procedures in the schedule of events for each patient. If a patient misses a study visit for any reason, the visit should be rescheduled as soon as possible. Patients are permitted to return to the clinical site for an unscheduled visit and have a dose decrease between 2 scheduled visits if deemed necessary only during the Titration-to-Effect Period of the study.

9.1 Study Periods and Visits

Screening occurs within 14 days before enrollment in the study; during the week prior to randomization (Day -5 to -1), patients will discontinue all current pain medications. Acetaminophen use is allowed (reference Section 8.8). The duration of treatment for this study is approximately 57 consecutive days. Clinic visits will take place on Days 1 (Baseline, Visit 2), 8, 15, 22, 29, 43, and 57 (Visit 8). Titration to the optimum dose will take place during the first 4 weeks of treatment (ending at Day 29 – Visit 6). A Follow-Up Visit will be performed 7 to 10 days after the last dose of study drug.

9.1.1 Screening and Washout

Each patient must be screened within 14 days before randomization in the study. The following procedures will be performed at Screening:

1. Obtain written informed consent.
2. Review inclusion/exclusion criteria.
3. Collect demographic information.
4. Record medical history (including duration of OA symptoms), and prior and current therapies (e.g., prescription and non-prescription medications).
5. Identify the index joint for the study.
6. Review how to complete assessment of pain intensity for the identified joint using the NRS.
7. Obtain a pain intensity score for the index joint using the NRS.
8. Review with the patient how to complete the WOMAC and Patient Global Impression of Change (PGIC).
9. Perform a physical examination including weight and height.
10. Collect vital signs (including body temperature).
11. Perform a 12-lead ECG.
12. Obtain blood and urine samples for drug screening, serum pregnancy (women of childbearing potential only), and clinical laboratory evaluations (including serum sodium measurement where sodium level must be ≤ 143 mmol/L). If sodium level is > 143 mmol/L,

then the patient can be retested in approximately 1 hour after being given a glass of water to drink.

13. If patient is eligible:
    a. Instruct patient to discontinue current pain medications 5 days prior to the Baseline Visit (Washout is Days -5 to -1). Instruct patients how to assess and record in the Patient Diary their pain intensity score and number of rescue medication tablets taken each evening for the 7 days prior to the Baseline Visit.
    b. Dispense rescue medication (acetaminophen).
    c. On Day -7, contact the patient to remind him or her about the washout week and the collection of daily pain scores.
    d. Schedule Visit 2 (Baseline; Day 1).

9.1.2 Baseline (Visit 2)

Baseline is defined as Day 1 (Visit 2). The following procedures will be performed at baseline:

1. Obtain a blood sample for serum sodium (sodium level must be ≤ 143 mmol/L) prior to dispensing study medication). If sodium level is > 143 mmol/L, then the patient can be retested in approximately 1 hour after being given a glass of water to drink.
2. Perform urine pregnancy test for female patients of childbearing potential.
3. Record any changes in prior and current therapies (e.g., prescription and non-prescription medications).
4. Assess vital signs.
5. Assess and record any AEs that have occurred since the last evaluation. Those will be recorded as medical history.
6. Perform drug accountability and, if necessary, counsel on compliance.
7. Review NRS data in the patient diary (Day -7 to Day -1) to calculate the Baseline NRS score and determine study eligibility. (The patient must have 4 pain scores at the index joint ≥ 5 for 4 or more of the last 7 days, with 2 consecutive days ≥ 5 immediately prior to randomization).
8. Review inclusion/exclusion criteria.
9. If patient is eligible:
    a. Assign the next patient number.
    b. Obtain blood samples for clinical laboratory evaluations including serum sodium.
    c. Have the patient complete the WOMAC.
    d. Dispense study medication and administer the first dose.
    e. Instruct patient on the use of rescue medication and fluid replacement.
    f. Review the PRO assessments and the recording of information in the patient diary.
    g. Schedule Visit 3 (Day 8) and instruct the patient to discontinue acetaminophen at least 12 hours prior to the clinic visit.

9.1.3 Titration Period

Patients will return to the clinic on Days 8, 15, 22, and 29 (±1 day), during which dose of CR845 will be titrated to the optimal level for each patient, based on tolerability and efficacy.

9.1.3.1 Day 8 (Visit 3)

Patients will return to the clinic on Day 8 (±1 day). The following procedures will be performed:

1. Perform drug accountability and, if necessary, counsel on compliance.
2. Record any changes in current therapies (e.g., prescription and non-prescription medications).
3. Assess vital signs.
4. Assess and record AEs occurring since the last evaluation.
5. Administer WOMAC.
6. Collect daily diaries (average pain intensity NRS scores, use of study drug and rescue medication).
7. Obtain a blood sample for serum sodium.
8. Review all outcome scores, use of rescue medication, and any AEs experienced during the prior week and determine if patient should remain at current dose level or be escalated to the next higher dose level. Enter this into the IVRS/IWRS to obtain the dosing kit number corresponding to the appropriate dose.
9. Schedule the next visit and instruct the patient to discontinue acetaminophen at least 12 hours prior to the clinic visit.
10. Dispense study and rescue medication for the next week.

9.1.3.2 Days 15 and 22 (Visits 4 and 5)

Patients will return to the clinic on Days 15 and 22 (±1 day). The following procedures will be performed:

1. Perform drug accountability and, if necessary, counsel on compliance.
2. Record any changes in current therapies (e.g., prescription and non-prescription medications).
3. Assess vital signs.
4. Assess and record AEs occurring since the last evaluation.
5. Administer WOMAC.
6. Collect daily diaries (average pain intensity NRS scores, use of study drug and rescue medication).
7. Obtain a blood sample for serum sodium (Days 15 and 22).
8. Review all outcome scores, use of rescue medication, and any adverse events experienced during the prior week and determine if patient should:
    a. Remain at the current dose level
    b. Be escalated to the next higher dose level

c. Be decreased to the previous dose level.

9. Enter dose level into the IWRS.
10. Schedule the next visit and instruct the patient to discontinue acetaminophen at least 12 hours prior to the clinic visit.
11. Dispense study and rescue medication for the next week

9.1.3.3 Day 29 (Visit 6)

Patients will return to the clinic on Day 29 (±1 day). The following procedures will be performed:

1. Perform drug accountability and, if necessary, counsel on compliance.
2. Record any changes in current therapies (e.g., prescription and non-prescription medications).
3. Assess vital signs.
4. Assess and record AEs occurring since the last evaluation.
5. Administer WOMAC.
6. Collect daily diaries (average pain intensity NRS scores, use of study drug and rescue medication).
7. Obtain a blood sample for serum sodium.
8. Review all outcome scores, use of rescue medication, and any adverse events experienced during the prior week and determine if patient should:
    a. Remain at the current dose level
    b. Be decreased to the previous dose level.
9. Enter this into the IWRS. *Please note that this is the final titration point.* The dose level determined here will be used during the 4-week Maintenance Treatment Period.
10. Schedule the next visit and instruct the patient to discontinue acetaminophen at least 12 hours prior to the clinic visit.
11. Dispense study and rescue medication for the next 2 weeks.

9.1.4 Maintenance Treatment Period

9.1.4.1 Day 43 (Visit 7)

Patients will return to the clinic on Day 43 (± 2 days). The following procedures will be performed:

1. Perform drug accountability and, if necessary, counsel on compliance.
2. Record any changes in current therapies (e.g., prescription and non-prescription medications).
3. Assess vital signs.
4. Assess and record AEs occurring since the last evaluation.

5. Administer WOMAC.
6. Collect daily diary (average pain intensity NRS scores, use of study drug and rescue medication).
7. Obtain a blood sample for serum sodium.
8. Schedule the next visit and instruct the patient to discontinue acetaminophen at least 12 hours prior to the clinic visit.
9. Dispense study and rescue medication for the next 2 weeks.

9.1.4.2 Day 57 (Visit 8) or Early Termination

Patients will return to the clinic on Day 57 (± 2 days) (Visit 8) or upon early termination from the study. The following procedures will be performed:

1. Collect the bottle of study medication, whether partly used, unused, or empty.
2. Perform drug accountability.
3. Record any changes in current therapies (e.g., prescription and non-prescription medications).
4. Assess vital signs (including body temperature).
5. Perform physical examination and record any changes from Screening.
6. Perform a 12-lead ECG.
7. Assess and record AEs occurring since the last evaluation.
8. Perform WOMAC.
9. Perform the PGIC.
10. Collect daily diary (average pain intensity NRS scores, use of study drug and rescue medication).
11. Obtain a blood sample for clinical laboratory evaluations and serum sodium measurement.
12. Schedule Visit 9 (Follow-up Visit; 7 to 10 days after last dose) and instruct the patient to resume pain medications as needed.

9.1.5 Follow-Up Evaluation (Visit 9)

At 7 to 10 days after the last dose of study medication, the following procedures will be performed:

1. Measure vital signs (blood pressure and heart rate).
2. Assess and record AEs occurring since the last evaluation. If any AEs are ongoing at this visit, telephone the patient 30 days after the last dose to assess and record additional updates to these AEs.
3. If not collected at Visit 8, collect the bottle of study medication, whether partly used, unused, or empty.

9.1.6 Unscheduled Visits

Unscheduled visits may be necessary for outstanding, unresolved TEAEs. Additional safety laboratory or clinical evaluations will be at the discretion of the Investigator.

9.2 Assessments

9.2.1 Efficacy Evaluations

9.2.1.1 Pain Intensity Numerical Rating Scale

Joint pain intensity will be assessed daily using an 11-point NRS[2] (see Appendix 2). The patient will rate his or her index joint pain intensity using the following question: "On a scale from 0 to 10, where 'zero' represents 'no pain' and '10' represents 'the worst possible pain,' how would you rate the average pain that you experienced in the last 24 hours?"

Daily assessment and recording of joint pain should be performed at the same time each day at approximately 6:00 pm, when possible. Patients will review their joint pain/diary data with the appropriate study site personnel during their clinic visits.

9.2.1.2 Western Ontario and McMaster Universities Osteoarthritis Index

The WOMAC Index is a self-administered assessment used to measure pain, stiffness, and physical function in patients with osteoarthritis (Appendix 3). It is considered to be a reliable and valid instrument.[3,4]

The WOMAC Index contains 24 questions across 3 different sub-scales (pain, stiffness, and function). Patients will complete the WOMAC at each clinic visit starting with the Baseline Visit.

9.2.1.3 Patient Global Impression of Change

The PGIC is a self-administered instrument that measures the patient's overall impression of his/her OA on a 7-point scale where 1 = "Very much improved" and 7 = "Very much worse" (see Appendix 4).

Patients will be asked the complete the following statement: "Since the start of the study, my osteoarthritis is:" using one of the following response options:

1. Very much improved
2. Much improved
3. Minimally improved
4. No change
5. Minimally worse
6. Much worse
7. Very much worse

The PGIC will be completed by the patient during the clinic visit on Day 57 (or early termination).

9.2.2 Safety Evaluations

The following safety measures will be assessed for all patients:

- Physical examination
- Vital signs
- 12-lead ECG
- Clinical laboratory evaluations (including serum sodium levels)
- Incidence and severity of AEs

9.2.2.1 Physical Examination

A physical examination will be performed at the time of Screening and on Day 57 or early termination. Findings at Screening will be reported as Medical History. New Findings or changes from the previous physical exam will be reported as AEs.

9.2.2.2 Vital Signs

Vital signs at the Screening visit (blood pressure and heart rate) will be conducted in both the supine and standing positions. For the purpose of these assessments, patients should be assessed in the supine position first and then, after sitting up for at least 1-minute, should be standing for at least 3 minutes prior to measuring blood pressure or heart rate.

Vital signs for the remainder of the study will be conducted with the patient at rest in the seated position. Vital signs will be assessed at each clinic visit.

Body temperature will be assessed at Screening and Day 57 (or early termination) only.

9.2.2.3 Electrocardiogram

A 12-lead ECG will be performed during the Screening visit and on Day 57.

9.2.2.4 Clinical Laboratory Assessments

Samples for the following laboratory tests will be collected at the time points specified in the schedule of events (Section 15).

Hematology	Hemoglobin, hematocrit, red blood cell (RBC) count, RBC indices, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelet count (or estimate), white blood cell (WBC) count including differential.
Serum Chemistry	Total bilirubin, ALT, AST, glucose (fasting/non-fasting), serum creatinine, BUN, electrolytes (sodium, potassium, chloride, and calcium), alkaline phosphatase, gamma glutamyl transferase, and creatinine.
Pregnancy Test	For female patients of childbearing potential, a serum pregnancy test will be conducted at Screening and a urine pregnancy test will be conducted at the Baseline visit prior to the administration of study drug.
Urine Drug Screen	Amphetamines, barbiturates, benzodiazepines, cocaine, opioids, phencyclidine (PCP), and tetrahydrocannabinol (THC).

Serum Sodium	Serum sodium levels will be measured at each clinic visit.

Blood samples for hematology and serum chemistry will be sent to a central laboratory for analysis. Urine drug screens, pregnancy tests, and sodium levels will be conducted at the study sites.

9.2.3 Management of Fluid Balance

Fluid management for this study will be achieved with specific recommendations for PO intake of fluid during the first 2 days of treatment and *ad libitum* afterwards. In general, patients should be instructed to drink fluids if they feel they are voiding more than usual.

Preferred oral fluids for this study are vitamin, flavored, spring, or tap water, depending upon the patient's preference. Caffeinated beverages should be minimized during the first day of treatment.

10. SAFETY DEFINITIONS, REPORTING AND MONITORING

10.1 Definition of Adverse Events

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product, and does not necessarily have a causal relationship with the treatment. An AE can be any unfavorable and unintended sign (e.g., including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study drug, whether or not it is considered to be study drug related.

An AE also includes any worsening (i.e., any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the Definition of Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in **death**
- Is **life threatening**. Life-threatening means that the patient was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that hypothetically might have caused death had it occurred in a more severe form
- Requires **inpatient hospitalization** or prolongation of existing hospitalization. Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected manner during the study (e.g., surgery performed earlier than planned)
- Results in persistent or significant **disability/incapacity**, defined as a substantial disruption of a patient's ability to conduct normal life functions
- Is a **congenital anomaly/birth defect**
- Is an **important medical event.** An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs.

Severe vs. Serious AEs: The term “severe” is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as “serious,” which is based upon patient outcome or reaction criteria usually associated with events that pose a threat to a patient’s life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

10.1.1 Recording and Reporting Adverse Events

All AEs and SAEs must be recorded on the eCRF and in the patient's source documents. Laboratory evaluations, fluid imbalance, outcome of a physical examination, vital signs, or ECG abnormalities are to be recorded as AEs only if they are clinically relevant.

All SAEs, regardless of assessment of causal relationship to study drug, must be reported to the Sponsor (or designee) as follows:

- Telephone the Sponsor (or designee) at the contact information provided in the SAE completion guidelines, within 24 hours of learning of the event.
- Fax the completed SAE form to the Sponsor (or designee) at the contact information provided in the SAE completion guidelines, within 24 hours of learning of the event.

CARA will provide the Investigators with blank SAE forms that are to be completed when reporting an initial or follow-up SAE. Information not available at the time of the initial report must be documented on a follow-up SAE form. Substantiating data such as relevant hospital or medical records and diagnostic test reports may also be requested.

The Investigator must promptly report to the Institutional Review Board (IRB) all unanticipated problems involving risks to patients. This includes death from any cause and all SAEs related to the use of the study drug. It is recommended that all SAEs be reported to the IRB, regardless of assessed causality. Further details will be given in the Safety Management Plan.

10.1.2 Deaths

Any AE that results in death is considered an SAE. Deaths that occur from the time the patient signs the informed consent form (ICF) until 30 days after the completion of dosing must be reported to the appropriate IRB and to the Medical Monitor at CARA (or designee) within 24 hours of learning of the death. The reporting procedures detailed in Section 10.1.1 should be followed.

Any available autopsy reports and relevant medical reports must be sent to the Sponsor (or designee) as soon as possible.

10.1.3 Pregnancy and Other Events that Require Accelerated Reporting

The following events also require reporting to the Sponsor (or designee) within 24 hours of learning of the event:

- **Overdose:** Accidental or intentional overdose of at least 2 times the study/recommended dose of study drug/concomitant medication, if associated with an AE. Accidental or intentional administration of the study drug at a frequency higher than that allowed by the study protocol, if associated with an AE.
- **Malignancy:** Any diagnosis (excluding non-melanoma skin cancer) during the study.
- **Pregnancy:** Although it is not considered an AE, it is the responsibility of the Investigator to report to the Sponsor (or designee), by telephone within 24 hours, any pregnancy occurring in a female patient or female partner of a male patient, during the

study or within 85 days following the last dose of study drug. The Sponsor will provide the Investigator with a Pregnancy Tracking Form that is to be completed by the study site on a monthly basis and faxed to the Sponsor (or designee). The Investigator will follow the pregnancy until delivery or longer. If the pregnancy continues to term (delivery), the health of the infant must also be reported to the Sponsor (or designee).

10.2 Adverse Event Identification and Assessment

Adverse events are illnesses or signs/symptoms that ***appear or worsen*** during the testing of a drug any time after the first dose is administered, whether or not considered related to the investigational product, including side effects, injury, toxicity, or hypersensitivity reactions.

Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states should also be recorded. In order to avoid vague, ambiguous, or colloquial expressions, AEs should be recorded in standard medical terminology rather than the patient's own words. Signs and symptoms should be reported individually unless, in the judgment of the Investigator, they can be grouped under an inclusive term (e.g., gastroenteritis in lieu of abdominal pain, nausea, vomiting, and diarrhea).

A pre-existing condition is a condition that is present prior to signing informed consent. For instance, this would include in this definition the discovery of an unexpected cancer following a laparoscopic hysterectomy. A worsening of a pre-existing condition should be captured as an AE if the frequency, intensity, or character of the condition worsens during the study period. Adverse events occurring after signing of the ICF but prior to the first administration of the study drug should be reported as medical history.

During the Screening process, any physical examination abnormalities deemed to be clinically significant by the Investigator should be recorded as Baseline conditions and recorded as the medical history. These will not be captured as AEs. After the first dose of study drug, any physical examination change deemed to be clinically significant by the Investigator that meets the definition of an AE must be recorded and documented as a TEAE.

Abnormal laboratory tests at Screening or Baseline assessed as clinically significant should not be reported as AEs but as medical history.

All abnormal laboratory test results that are clinically significant (including those reported as chronically typical for the patient) must comply with exclusionary criteria; otherwise, the Medical Monitor must be contacted to decide whether to continue the participation of the patient in the study. A laboratory abnormality should be documented as an AE if it is considered by the Investigator to be a clinically significant adverse change from Baseline.

Any AE that results in hospitalization or prolonged hospitalization should be reported as an SAE.

An abnormal result of a diagnostic procedure should be captured as an AE if the abnormality:

- Results in study withdrawal
- Is associated with signs or symptoms
- Is considered by the Investigator to be of clinical significance.

The underlying diagnosis will be captured as the AE, not the procedure itself.

Overdose is defined as an accidental or intentional exposure to study drug at a dose higher than specified in the protocol or higher than the known therapeutic dose. An overdose of study drug must be reported as a protocol deviation. If the overdose is associated with clinical signs or symptoms, then these should be captured as AEs. An overdose is not expected to occur in this study based on the protocol design.

10.2.1 Evaluation of Severity

Adverse events will be graded according to the following scale:

- **Mild:** Transient or mild discomfort (< 48 hours); no medical intervention/therapy required. Does not interfere in a significant manner with the patient's normal functioning level.
- **Moderate:** Mild to moderate limitation in activity – some assistance may be needed; minimal medical intervention/therapy may be required. Produces some impairment of functioning but is not hazardous to health.
- **Severe:** Produces significant impairment of functioning or incapacitation and is a definite hazard to the patient's health. Treatment for symptom may be given and/or patient hospitalized.

If the intensity of an AE changes, the maximum severity for the event should be listed. If the intensity category changes over a number of days, these mini-events or changes should be recorded separately (i.e., having distinct onset dates).

10.2.2 Evaluation of Causality

The relationship to treatment will be determined by the Investigator and reported on the eCRF and/or SAE form, as appropriate. The following terms will be used:

- **Not Related:** likely or clearly due to causes other than the study drug
- **Related:** possibly, probably, or definitely related to the study drug

10.3 Adverse Event Follow-up and Reporting

10.3.1 Investigator Alert Notification

CARA or its designee will inform all Investigators participating in this clinical trial, as well as in any other clinical trial using the same investigational drug, of any SAE that meets the relevant requirements for expedited reporting (an AE that is serious, unexpected based on the Investigator's Brochure, and has a reasonable suspected causal relationship to the medicinal/investigational product).

10.3.2 Adverse Event Follow-up

All patients with documented AEs (including SAEs) will be followed by the Investigator until the AE resolves, resolves with sequelae, decreases in severity to a clinically insignificant level, is otherwise explained by a medical condition, or is not possible to follow-up (document) due to loss of follow-up or the death of the patient.

10.3.3 Adverse Event Documentation

All AEs, including observed, elicited, or volunteered problems, complaints, or symptoms, are to be recorded on the AE page in the patient's eCRF.

The need to capture this information is not dependent upon whether AEs are associated with use of investigational product.

Each AE is to be evaluated for date/time of onset, duration, intensity, and causal relationship with the study drug or other factors.

At every study visit, the Investigator or designee must document new AEs and the outcome of ongoing AEs.

All SAEs will be documented on the SAE form.

10.3.4 Serious Adverse Event Reporting

10.3.4.1 Notification and Documentation from the Investigator to the Sponsor

The Investigator will immediately, and in no case later than 24 hours of awareness, notify CARA by telephone if a death or life-threatening event occurs, whether related or unrelated to the study drug. In this instance, an SAE report form will also be completed by the Investigator immediately (and in no case later than 24 hours of site awareness). Serious AEs other than death and immediately life-threatening events, regardless of relationship to study drug, will be reported to CARA by telephone and email within 24 hours (and in no case later than 72 hours [in case of weekends]) of Investigator awareness, and the SAE form will be completed within 48 hours of becoming aware of the event.

The Investigator will forward details of SAE(s) to the Sponsor within 2 working days for an expedited report and 3 working days for a non-expedited report.

The Sponsor may contact the Investigator to obtain more information or clarification on the SAE reported. Other supporting documentation of the SAE requested by the Sponsor should be provided as soon as possible. The Sponsor contact person is:

Heidi Schecodnic, M.D., Medical Director, Medical Affairs
INC Research, LLC
3201 Beechleaf Ct., Suite 600
Raleigh, North Carolina 27604
Office: 919-745-2785 Mobile: 984-242-6534
heidi.schecodnic@incresearch.com

The initial telephone report from the Investigator to the Sponsor of the SAE will include all available information in order to assist the Sponsor in submitting SAEs (e.g., "Investigational New Drug [IND] Safety Report") to the appropriate regulatory agencies as defined by country-specific regulations. Initial minimal information required will include:

- An identifiable patient
- An identifiable reporter

- A suspect drug/product
- An adverse drug reaction

An SAE eCRF page must be completed in the electronic database and supporting documentation given to the Sponsor.

Follow-up information to a safety report shall be submitted as soon as the relevant information (e.g., discharge summary) is available. A Follow-up SAE report must be completed and transmitted via facsimile to the Sponsor or designee as soon as the information is available for relevant follow-up information only. For non-relevant additional information, the Investigator should send information in a timely manner via facsimile to the Sponsor. The Sponsor's Medical Monitors or designee will contact the Investigator to obtain more information or clarification on the SAE reported.

10.3.4.2 Reporting to Regulatory Authorities

All expedited SAEs will be reported to the regulatory authorities per regulatory requirements.

Adverse events that are serious and related to the study drug and unexpected must be reported to the regulatory authorities on an expedited basis as an IND Safety Report. Of these IND safety reports, those with the outcome of death or life threatening will be reported by the Sponsor to the regulatory authorities within 7 calendar days (from the date of SAE notification); and all the other expedited IND safety reports will be reported to the regulatory authorities within 15 calendar days (from the date of SAE notification).

The Sponsor will also notify the participating Investigator of all IND Safety Reports to ensure prompt notification of significant new adverse effects or risks with respect to the drug. This notification will occur as soon as possible and in compliance with country-specific regulations.

Per regulatory requirement, the Investigator should promptly report all SAEs, in addition to all changes in research activity, protocol violations, and unanticipated problems involving risk to human patients or others, to their IRB.

All other SAEs that do not fulfill the expedited reporting criteria are to be included in the IND Annual Report.

11. STATISTICAL METHODS

11.1 General Considerations

The following section summarizes the statistical methods that will be used in the analysis of the clinical data from this study. A statistical analysis plan (SAP) with further detail will be developed and finalized prior to unblinding of the study. If differences occur between analyses described in the final SAP and the current protocol, those found in the SAP will assume primacy.

Unless otherwise noted, continuous variables will be summarized using the number of non-missing observations, mean, standard deviation, median, minimum, and maximum; categorical variables will be summarized using the frequency count and the percentage of patients in each category. In addition to the descriptive summaries, pertinent data listings will be provided to facilitate case studies.

Statistical significance will be declared for all hypothesis testing if the unadjusted 2-sided probability value is < 0.05. Tests for interaction among the sites will be performed at the 0.1 alpha level. All computations will be performed using SAS® (Version 9.2 or higher).

11.2 Determination of Sample Size

Approximately 405 patients with OA of the hip and knee will be randomized in a 2:1 ratio (270 to CR845 and 135 to placebo) at approximately 40 sites in the United States.

[redacted]

[redacted]

11.4 Analysis Populations

Three patient analysis populations are defined as follows:

- **Safety Population**: All randomized patients who received at least 1 dose of double-blind study drug will be included in the safety evaluation.
- **Full Analysis Population (FAP):** All randomized patients who received at least 1 dose of double-blind study drug will be included in the safety evaluation. The FAP and the Safety populations are identical.
- **Per Protocol (PP):** All randomized patients in the FAP without any major protocol violations that could affect the efficacy analyses. The criteria for determining what constitutes a major protocol violation will be defined prior to database lock and the breaking of the blinded treatment assignment code.

Membership in the analysis populations will be determined prior to unblinding the data and will be detailed in the SAP.

11.5 Patient Accounting and Study Disposition

11.5.1 Patient Disposition

A complete accounting of patient participation in the study will display the number of patients that were enrolled and the number and percentage of patients that:

- Were screen failures
- Were randomized
- Are included in each analysis population
- Have completed or discontinued study drug early

In addition, the reason for early study termination will be summarized separately and presented using counts and percentages.

11.5.2 Protocol Deviations

Protocol deviations or violations will be identified in several ways: through programmatic checks, through medical reviews, and by clinical research associates during site monitoring. They will be classified as minor or major prior to the database lock and included in the SAP.

Major protocol deviations/violations will be summarized by treatment group. All protocol deviations will be listed.

Patients with major protocol violations that affect efficacy will be excluded from analysis for the PP population.

11.6 Baseline Patient Data

11.6.1 Demographic and Other Baseline Characteristics

The following demographic variables will be summarized by treatment group and overall: age, sex, race, ethnicity, height, weight, BMI, and duration of time with OA.

11.7 Study Drug Accountability

A data listing of the study drug dispensed and returned will be provided.

Patients will be considered noncompliant if they miss 2 or more doses during the Titration-to-Effect period.

Patients will be considered noncompliant if their overall study drug use is not within 80% to 110% (inclusive) of the expected drug use during the Maintenance Treatment period.

The expected number of tablets to be taken will be calculated based on the duration of treatment. The count and percentage of patients compliant with study drug will be summarized by treatment group (CR845 vs. placebo).

The number of patients who titrated to Level 1 (CR845 1 mg or matching placebo), Level 2 (CR845 2.5 mg or matching placebo) or Level 3 (CR845 5 mg or matching placebo) will be summarized. In addition, the average dose of each patient during the study will be calculated and presented for each treatment group.

The number and percentage of patients exposed to double-blind study drug for overlapping time intervals (e.g., any exposure, ≥ 1 week, ≥ 2 weeks, ≥ 4 weeks, ≥ 8 weeks) will be calculated by treatment group. Descriptive statistics (mean, standard deviation (SD), median, minimum, maximum) will be provided to summarize the length of exposure (in days) to each treatment.

Dosing details and any deviations from the planned dose will be listed.

11.8 Efficacy Analyses

All efficacy analyses will be conducted on the FAP. An analysis of the primary efficacy variable using the PP population may be performed if a significant number (≥ 20%) of the patients in the FAP are regarded as major protocol violators that would affect the evaluation of efficacy and are excluded from the PP population. The need for a PP population analysis will be examined prior to database unblinding. All hypothesis tests will be 2-sided at the α=0.05 level.

11.7.1 Primary Efficacy Variable

The primary efficacy variable is the weekly mean pain intensity score calculated using the 'average pain over the last 24 hours' scores collected in the daily diaries using an 11-point scale where 0 = no pain, and 10= pain as bad as you can imagine. The weekly mean pain intensity

score will be defined as the sum of non-missing daily "average pain over the last 24 hours" scores reported during that week (Days 1-7, Days 8-14, Days 15-21, … , Days 50-56) divided by the number of days with non-missing scores for that week. If a patient reports less than 3 days of pain scores during a week, the weekly mean pain intensity score will be set to missing.

The primary efficacy endpoint is defined as the change from baseline at Week 8 with respect to the weekly mean of the daily 24-hour pain intensity in at the index joint.

The primary efficacy variable will be analyzed using a mixed effect model with repeated measures (MMRM). The model will contain treatment (placebo vs CR845), treatment-by-week interaction as fixed effects, baseline value and OA joint (hip vs knee) as covariates, and patient as a random effect. The baseline score will be calculated as the average of the 4 pain scores collected during the Screening period that qualified the patient for randomization (inclusion criteria 12). The treatment difference between CR845 (across all doses) and placebo at Week 8 (the primary efficacy endpoint) will be estimated as the simple contrast in the treatment effect. The 2-sided 95% confidence interval, based on the difference in the least squares means between the 2 treatment groups (CR845 vs placebo) will be presented.

The MMRM model will be implemented using SAS PROC MIXED. A restricted maximum likelihood (REML) method will be used . An appropriate covariance matrix will be used to model the within patient errors. The use of an unstructured covariance matrix structure as well as other structures, such as spatial patterns, that require fewer parameters (Toeplitz, autoregressive [1], or compound symmetry) will be examined. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom and adjust standard errors.

For the primary efficacy analysis, the treatment of missing data will be addressed using pattern mixture model methodology. Within each treatment, 4 data patterns will be defined as follows:

- Pattern 1: will include patients who completed treatment on study drug
- Pattern 2: will include patients who discontinue treatment early due to AEs
- Pattern 3: will include patients who discontinue treatment early due to lack of therapeutic efficacy (LOTE)
- Pattern 4: will include patients who discontinue treatment early due to reasons other than AE event or LOTE.

The pattern mixture model methodology will be implemented using SAS procedures MI and MIANALYZE. Specifically, the following steps will be followed:

- Intermittent missing data will first be imputed using the Markov Chain Monte Carlo (MCMC) method implemented with the SAS MI procedure, which is appropriate for non-monotonic missing data.
- Data for patients who discontinue early will be multiply imputed using multiple calls of the SAS MI procedure.

- If the patient discontinues due to AE (pattern 2) or LOTE (pattern 3), then missing data will be assumed to follow a distribution similar to the baseline values observed in the patient's randomized treatment.
- If the patient discontinues due to reasons other than AE or LOTE (pattern 4), at each time point, missing data will be assumed to follow a distribution similar to scores for patients who are still in the study and randomized to the same treatment group.

- Results of the MMRM on the multiply imputed data will be summarized using the SAS MIANALYZE procedure.

Three sensitivity analyses (described below) will be conducted to assess the impact of the treatment of missing data on the study results. These sensitivity analyses may not necessarily reach statistical significance at the 5% level. However, a consistency of treatment effect (similar estimate of CR845 mean relative to placebo) is expected across the primary and all sensitivity analyses.

Sensitivity analysis 1 (Multiple Imputation Missing at Random)

This sensitivity analysis assumes that patients with missing data follow the same trajectory as other patients in their respective treatment arm that have complete data.

- Intermittent missing data will first be imputed using the MCMC method implemented with the SAS MI procedure, which is appropriate for non-monotonic missing data.
- Data missing after patients discontinue treatment early will then be multiply imputed with the SAS MI procedure using a method appropriate for monotone missingness (e.g., regression statement). At each time point, missing data will be assumed to follow a distribution similar to scores for patients who are still in the study and randomized to the same treatment group.
- Results of the MMRM on the multiply imputed data sets will be summarized by the SAS MIANALYZE procedure.

Sensitivity analysis 2 (Multiple Imputation, Missing Not at Random, Placebo-based Imputation)

This sensitivity analysis assumes that patients in the active treatment group who discontinue early will have the same evolution, after treatment is stopped, as patients in the placebo group (who are not exposed to treatment by definition). Patients who discontinue treatment early in the placebo group are assumed to behave as the placebo patients that remain in the study.

- Intermittent missing data will first be imputed using the MCMC method implemented with the SAS MI procedure, which is appropriate for non-monotonic missing data.
- Data missing after patients discontinue treatment early will be multiply imputed using multiple calls of the SAS MI procedure. At each time point, missing data will be imputed using data from patients in the placebo group that have complete data at that time.
- Results of the MMRM on the multiply imputed data sets will be summarized by the SAS MIANALYZE procedure.

Sensitivity analysis 3 (Multiple Imputation, MNAR, Hybrid BOCF /LOCF):

This sensitivity analysis makes different assumptions about the pain trajectory of patients who discontinue study drug early depending on the reason for discontinuation. For patients who discontinue due to AE or reasons other than AE or LOTE, assumptions are similar to the ones made for the primary efficacy analysis. It is plausible that patients who discontinue due to LOTE experience worsening pain scores after randomization; in this case, their last observed pain scores would be higher (worse) that their baseline pain scores. This sensitivity analysis assumes that missing data for these patients is similar to observed pain scores for patients who discontinue due to LOTE but are still in the study.

- Intermittent missing data will first be imputed using the MCMC method implemented with the SAS MI procedure, which is appropriate for non-monotonic missing data.
- Data for patients who discontinue early will be multiply imputed using multiple calls of the SAS MI procedure.
    - If the patient discontinues due to AE (pattern 2), missing data will be assumed to follow a distribution similar to the baseline values observed in the patient's randomized treatment.
    - If the patient discontinues due to LOTE (pattern 3), at each time point, missing data will be assumed to follow a distribution similar to scores for patients who are still in the study and randomized to the same treatment group.
    - If the patient discontinue due to reasons other than AE or LOTE (pattern 4), at each time point, missing data will be assumed to follow a distribution similar to scores for patients who are still in the study and randomized to the same treatment group.
- Results of the MMRM on the multiply imputed data will be summarized using the SAS MIANALYZE procedure.

Finally, an MMRM analysis using observed data only will be provided as a reference.

11.8.1 Secondary Efficacy Variables

Western Ontario & McMaster Osteoarthritis (WOMAC) Index

The change from baseline in the WOMAC Index total score will be analyzed using an MMRM with treatment (placebo vs CR845) and treatment-by-week interaction as fixed effects, baseline value and OA joint (hip vs knee) as covariates, and patient as a random effect. The primary comparison between groups will be based on estimates and contrasts for the weeks 4, 6, and 8 means. The comparison at week 8 will be viewed as secondary. A 95% CI will be constructed for the weeks 4, 6 and 8 mean differences between CR845 and placebo based on the MMRM.

The MMRM model will be implemented using SAS PROC MIXED. REML will be used. An appropriate covariance matrix will be used to model the within patient errors. The use of an unstructured covariance matrix structure as well as other structures, such as spatial patterns, that require fewer parameters (Toeplitz, autoregressive [1], or compound symmetry) will be

examined. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom and adjust standard errors.

Data missing after early discontinuation will be treated using the same pattern mixture methodology as the one implemented for the primary efficacy analysis. In addition, an MMRM analysis using observed data only (i.e., no imputation) will be presented.

WOMAC Pain Intensity, Stiffness, and Function Sub-scales

The change from baseline in the WOMAC sub-scales for pain intensity, stiffness and function will be analyzed using an MMRM model similar to the one presented above for the WOMAC index total score. Data missing after early discontinuation will be treated using the same pattern mixture methodology as the one implemented for the primary efficacy analysis. In addition, an MMRM analysis using observed data only (i.e., no imputation) will be presented.

Treatment Pain Response

A patient's pain response to treatment is defined as the percent improvement from baseline with respect to the weekly mean of "average pain in the last 24 hours" pain score during the last week of the Maintenance Treatment Period (Week 8)

If a patient's mean weekly pain score during the last week of the Maintenance Treatment Period is greater than the baseline score (i.e., the patient has an increase in pain compared to baseline), his/her response to treatment will be assigned a value of 0. Patients who discontinue study drug early will be considered non-responders to treatment and will be assigned a pain response of 0.

A graph of percentage of patients who have a treatment pain response ≥ 10%, ≥ 20%, ≥ 30%, ≥40%, ≥ 50%, ≥ 60%, ≥70%, ≥ 80%, ≥ 90%, and ≥ 100% will be presented. In addition, the proportion of patients with a response to treatment that is ≥ 30% will be analyzed using logistic regression, including treatment, baseline pain score, and OA joint as independent variables. The cutoff of 30% was chosen as it has been shown to represent a clinically important improvement in pain. This analysis will be repeated for patients who have a response to treatment ≥ 50%.

Patient Global Impression of Change (PGIC)

The PGIC score collected at Week 8, or at the End of Treatment visit (for patients who discontinue treatment early) ranges from 1 (Very Much Improved) to 7 (Very Much Worse). The count and proportion of patients in each response category will be displayed for each treatment group. In addition, summary statistics (n, mean, standard error, median, minimum, and maximum) and 95% CI for the mean treatment response will be tabulated.

The proportion of patients with PGIC scores of "Very Much Improved" and "Much Improved" will be analyzed using logistic regression with treatment as a main effect, and OA joint as a covariate.

Supplemental Analgesic Medication Used

Acetaminophen is the only allowable rescue medication for pain beginning from Day -5 until the end of the Maintenance Treatment Period. Acetaminophen will be provided as 325-mg tablets with a maximum allowable dose of 8 tablets per day (given every 4 to 6 hours as needed).

However, the use of acetaminophen is not allowed for the 12 hours prior to a scheduled office visit until after the efficacy assessments have been completed, in order to minimize the confounding effects of rescue medication on these measures.

The average daily number of acetaminophen tablets used during the study will be calculated using data recorded in the patient diary as the sum of the total number of tablets used divided by the length of exposure (in days). The average daily number of acetaminophen tablets used during the Maintenance Treatment Period will be calculated using a similar algorithm. Descriptive statistics for each of these 2 variables (n, mean, SD, median, minimum, maximum) will be presented by treatment group.

Due to the nature of the data, the average daily number of analgesic rescue doses used (in this case acetaminophen) tends to have a large portion of zeroes (contributed by patients not taking any supplemental pain medication) followed by continuous distribution of non-zero values. Therefore, the supplemental pain medication for OA will be summarized categorically into the following classes: (1) no supplemental acetaminophen tablets, (2) 0 to ≤ 0.5 tablets, (3) > 0.5 to ≤ 1.0 tablets, (4) > 1.0 to ≤ 2.0 tablets, and (5) > 2.0 tablets. Upon review of the blinded data prior to database lock, the classes will be reviewed and if any adjustments are deemed necessary, the rationale and new categories will be documented in the final SAP.

The number and percentage of patients who withdraw from the study due to lack of analgesic efficacy will be tabulated for each treatment group and compared using a generalized linear model; the distribution of the data will be specified as binomial.

11.9 Safety

Analysis of all safety data will be performed on the safety population and will be presented based on the treatment received.

11.9.1 Adverse Events

All reported adverse events will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). Verbatim descriptions of the adverse event in addition to the SOC and the preferred term (PT) will be included in the patients' data listings.

Data for AEs will be analyzed using the treatment-emergent signs and symptoms philosophy. A TEAE is defined as an AE where:

- onset occurs during exposure to study medication or within 7 days after the last dose of study medication, having been absent prior to receiving study medication, or
- onset reoccurs during exposure to study medication or within 7 days after the last dose of study medication, having been present but stopping prior to receiving study medication, or
- worsening in severity occurs during exposure to study medication relative to the pre-treatment state, when the AE is continuous.

All reported AEs (whether treatment-emergent or not) will be included in a by-patient AE listing. Only TEAEs will be included in summary tables. Adverse events that occur up to the follow-up visit will be counted as TEAEs. The incidence of TEAEs will be presented by the counts

and percentages of patients with AEs. A patient will be counted only once in the incidence count for a MedDRA PT, although a patient may have multiple occurrences (start and stop) of an event associated with a specific MedDRA PT.

Serious adverse events, AEs that lead to study drug or to study discontinuation, and AEs related to treatment will also be summarized. In addition, a table of TEAEs by severity and of TEAEs occurring in ≥ 5% of the patients in at least one treatment group will be presented.

If the severity or relationship to the study drug is missing, a worst-case scenario will be assumed (i.e., it will be set to severe or definitely related relationship). All SAEs will be tabulated overall and by severity and relationship to the study drug.

11.9.2 Prior and Concomitant Medications

Concomitant medications will be coded using the current version of the World Health Organization Drug Dictionary (WHO-DD). The number and percent of patients taking concomitant medications will be tabulated for each treatment group by appropriate WHO-DD classifications. Prior medications will be presented in a listing.

11.9.3 Clinical Safety Laboratory Evaluations

Mean changes from baseline to Day 57 will be presented for each of the laboratory parameters. Shift tables from baseline to Day 57 will be provided and abnormalities will be flagged (i.e., values above or below the reference ranges). The incidence of markedly abnormal laboratory results may be calculated. Additional analyses of liver function test will be completed to address the FDA guidance on the assessment of drug-induced liver injuries. Specifically, additional shift tables for AST, ALT and Total Bilirubin will be generated using the categories presented in Table 2 below.

Table 2 Categories for Shift Analysis of AST, ALT, and Total Bilirubin

AST/ALT	Total Bilirubin
≤ 1 x ULN	1 x ULN
> 1 - ≤ 3 x ULN	> 1 – 1.5 x ULN
> 3 - ≤ 5 x ULN	> 1.5 – 2.0 x ULN
> 5 - ≤ 10 x ULN	> 2.0 x ULN
> 10 - ≤ 20 x ULN	
> 20 x ULN	

For each time point, the proportion of patients who have a serum sodium value > 146 mmol/L in each treatment group will be tabulated. In addition, a listing including all patients who had at least one serum sodium measurement post treatment > 146 mmol/L will be prepared.

11.9.4 Vital Signs

Summary statistics will be presented for vital signs and mean changes from baseline to each of the time points. An analysis of abnormal and clinically notable vital sign changes will also be

conducted. Details of these analyses, in particular the definition of abnormal and clinically notable vital signs, will be included in the SAP.

11.9.5 ECGs

Electrocardiogram results at Baseline will be summarized as normal or abnormal. If a result is abnormal, the abnormality will be assessed as either clinically significant or not clinically significant.

12. STUDY CONDUCT

12.1 Sponsor and Investigator Responsibilities

12.1.1 Sponsor Responsibilities

The Sponsor is obligated to conduct the study in accordance with strict ethical principles (Section 13). The Sponsor reserves the right to withdraw a patient from the study (Section 7.4) to terminate participation of a study site at any time, and/or to discontinue the study (Section 13.6).

CARA agrees to provide the Investigator with sufficient material and support to permit the Investigator to conduct the study according to the study protocol.

12.1.2 Investigator Responsibilities

By signing the Investigator's Agreement (Appendix 5), the Investigator indicates that he/she has carefully read the protocol, fully understands the requirements, and agrees to conduct the study in accordance with the procedures and requirements described in this protocol.

The Investigator also agrees to conduct this study in accordance with all laws, regulations, and guidelines of the pertinent regulatory authorities, including and in accordance with the April 1996 International Conference on Harmonisation (ICH) Guidance for Industry E6 Good Clinical Practices (GCP), and in agreement with the 1996 version of the Declaration of Helsinki. While delegation of certain aspects of the study to subinvestigators and study coordinators is appropriate, the Investigator will remain personally accountable for closely overseeing the study and for ensuring compliance with the protocol and all applicable regulations and guidelines. The Investigator is responsible for maintaining a list of all persons that have been delegated study-related responsibilities (e.g., subinvestigators and study coordinators) and their specific study-related duties.

Investigators should ensure that all persons who have been delegated study-related responsibilities are adequately qualified and informed about the protocol, the study medication, and their specific duties within the context of the study. Investigators are responsible for providing CARA with documentation of the qualifications, GCP training, and research experience for themselves and their staff as required by the Sponsor and the relevant governing authorities.

To ensure compliance with the guidelines, the study will be audited by an independent person. The Investigator agrees, by written consent to this protocol, to cooperate fully with compliance checks by allowing access to all study documentation by authorized individuals.

12.2 Quality Control and Quality Assurance

The clinical monitors will follow written standard operating procedures as agreed to between the contract research organization (CRO) and the Sponsor. The monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements. Monitoring reports will be submitted to the Sponsor in a timely fashion.

12.2.1 Audits and Inspections

12.2.1.1 Source Documents and Access to Source Data/Documents

The site will maintain appropriate medical and research records for this trial, in compliance with ICH-GCP and regulatory and institutional requirements for the protection of confidentiality of participants. The Investigator must allow access to authorized persons or institutions to complete data-source verification. Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and participant files and records kept at the pharmacy, laboratories, or medical-technical departments involved in the clinical trial.

The investigational site will provide direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor and inspection by regulatory authorities.

12.3 Data Collection, Validation and Analysis

The data management coordinator will ensure that quality-assurance procedures are implemented, beginning with the data entry system and generation of data quality-control checks that will be run on the database.

12.4 Study Monitoring Plan

Monitoring and auditing procedures that comply with current GCP guidelines will be followed. On-site review of the eCRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed.

The study will be monitored by CARA or its designee. Monitoring will be done by personal visits from a representative of the Sponsor (site monitor) who will review patient enrollment, eCRFs, source documents, drug accountability records, and reporting and recording of AEs. The site monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent site visits and communications (letter, telephone, and facsimile).

12.5 Safety Monitoring Plan

Due to the controlled nature of this study and the limited exposure to study drug in this study, the safety risks to patients participating in this study should be minimal. The Investigators, as well as the CRO and the Sponsor's Medical Monitor, will closely monitor and assess the clinical safety and safety data from patients participating in the study. In addition, safety data will be reviewed periodically by an external independent data monitoring committee (IDMC).

12.6 Data Management and Record Keeping

12.6.1 Case Report Form Completion

Electronic case report forms (eCRFs) will be completed for each study patient. It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the patient's eCRF. Source documentation supporting the eCRF data should indicate the patient's participation in the study and should document the dates and details of study procedures, AEs, and patient status.

The Investigator or designated representative will complete the eCRF pages as soon as possible after information is collected, preferably on the same day that a study patient is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. An explanation should be given in the source document for all missing data.

The Investigator must sign and date the Investigator's Statement on the appropriate page of the eCRF to endorse the recorded data.

12.6.2 Data Management Responsibilities

All source documents and laboratory reports must be reviewed by the site clinical team and data-entry staff, who will ensure that they are accurate and complete. Adverse events must be graded, assessed for severity and causality, and reviewed by the Investigator or designee.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the Investigator. During the study, the Investigator must maintain complete and accurate documentation for the study.

12.7 Administrative Procedures

12.7.1 Study Records Retention

The Investigator will retain all study records according to ICH-GCP and applicable regulatory requirement(s). Records will be retained until notified by CARA in writing that the records may be destroyed. The Investigator shall take responsibility for maintaining adequate and accurate hard-copy source documents of all observations and data generated during this study, including any data clarification forms received from the Sponsor. Such documentation is subject to inspection by CARA, its representatives, and regulatory authorities. If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. If a custodial change or a change in record location occurs, CARA must be notified in writing.

12.7.2 Protocol Adherence

It is vital to the success of the study that the Investigator adheres to the details of the protocol, and keeps to a minimum the number of cases later classified as "incomplete," "unusable," or "not evaluable." If in the interest of safety and/or well-being of a particular patient, it is

necessary to depart from the protocol, then that protocol deviation will pertain to that individual patient only.

Protocol deviations due to lack of patient compliance must also be documented. All protocol deviations will be summarized in the final clinical study report.

The Clinical Monitor will review protocol deviations throughout the course of monitoring visits and document new findings of violations and deviations. The monitor will notify the Investigators of violations and deviations verbally or in writing. The IRB should be notified of all protocol violations and deviations in a timely manner according to IRB requirements.

12.8 Changes to the Protocol

This protocol cannot be altered or changed except through a formal protocol amendment, which requires the written approval of Cara. The protocol amendment must be signed by the Investigator and approved by the IRB or IEC before it may be implemented. Protocol amendments will be filed with the appropriate regulatory agency having jurisdiction over the conduct of the study.

12.9 Publication of Study Findings

All information regarding CR845 provided by CARA to the Investigator is privileged and confidential. By conducting this study, the Investigator affirms to the Sponsor that he/she will maintain, in strict confidence, information furnished by the Sponsor, including data generated from this study and preliminary laboratory results, except as exempted for regulatory purposes.

All data generated during the conduct of this study are owned by CARA. The Investigator agrees to use the information to accomplish the study and will not use it for other purposes without written permission from CARA. Partial or full data or results from this study cannot be published without express written consent from CARA. It is understood that there is an obligation to provide CARA with complete data obtained during the study. The information obtained from the clinical study will be used toward the development of CR845 and may be disclosed to regulatory authority, other Investigators, corporate partners or consultants as required.

13. ETHICS/PROTECTION OF HUMAN PATIENTS

This study will be conducted in compliance with the Declaration of Helsinki and its amendments, the ICH principles of GCP (including archiving of essential study documents), and the applicable regulations of the country in which the study is conducted.

13.1 Ethics

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki and all accepted amendments. The IRB will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of the patients. The study will only be conducted at a site where IRB approval has been obtained. The protocol, Investigator's Brochure (IB), informed consent, advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the Investigator.

If it is necessary to amend the protocol and/or ICF during the course of the study, the Investigator must ensure that the IRB reviews and approves these amended documents. No amendments to the study protocol should be made without the prior written agreement of both the Investigator and the Sponsor, and the IRB.

The Investigator will maintain documentation of the composition of the IRB as well as all correspondence with the IRB. The Investigator will comply with local requirements for routine reporting to the IRB as well as local and government requirements for notifying the IRB of SAEs. The Investigator will prepare a final study report and submit it to the IRB no later than 3 months after study completion. The Investigator will provide CARA or its designee copies of all IRB approval notices, correspondence, annual reports, and final study progress reports.

13.2 Good Clinical Practices

The study will be conducted in accordance with the ICH - GCP and the appropriate regulatory requirement(s). The Investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and IB. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files will be established at the beginning of the study, maintained for the duration of the study, and retained according to the appropriate regulations.

13.3 Institutional Review Board

Each participating IRB will be constituted and function per GCP guidelines to provide for the review and approval of this protocol and the associated informed consent documents. Any amendments to the protocol or consent materials must also be approved before they are placed into use.

A properly constituted, valid IRB must review and approve the protocol, ICF, and related patient information and recruitment materials before the start of the study.

13.4 Informed Consent Process

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. The Investigator or designee will discuss extensively with the participant patient the study risks and possible benefits of this therapy. Copies of the ICF detailing the risks and benefits of study participation will be provided to the participants and their families.

Informed consent forms describing in detail the study drug and study procedures/intervention and risks will be fully explained to the patient and written documentation of informed consent will be required prior to starting study agent/intervention. Informed consent forms will be IRB approved and the participant will be asked to read and review the document. Upon reviewing the document, the Investigator or designee will explain the research study to the participant and answer any questions that may arise. The participants will sign the ICF prior to any procedures being done specifically for the study. The participants should have sufficient opportunity to discuss the study and process the information in the consent process prior to agreeing to participate. The participants may withdraw consent at any time throughout the course of the trial. A copy of the ICF will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

Informed consent is required for all patients participating in this study. In obtaining and documenting informed consent, the Investigator should comply with applicable regulatory requirements and should adhere to GCP guidelines. Prior to the beginning of the trial, the Investigator should have the IRB written approval/favorable opinion of the written ICFs and any other written information to be provided to the participants. It is the responsibility of the Investigator to ensure that a signed ICF is obtained from the patient before any activity or procedure is undertaken that is not part of routine care.

13.5 Patient Confidentiality

In order to maintain patient privacy, all eCRFs, study drug accountability records, study reports, and communications will identify the patient by initials and the assigned patient number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or designee and regulatory authority access to the patient's original medical records for verification of data gathered on the eCRFs and to audit the data-collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Participant confidentiality is strictly held in trust by the participating Investigators, their staff, and the Sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participating patients.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party, without prior written approval of the Sponsor.

The Clinical Monitor or other authorized representatives of the Sponsor may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study.

13.6 Study Discontinuation

This study may be prematurely terminated if, in the opinion of the Investigator or CARA, there is reasonable cause. Written notification documenting the reason for study termination will be provided to the Investigator or CARA by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient data and/or data that cannot be evaluated
- Plans to modify, suspend, or discontinue the development of the study drug

Should the study be closed prematurely, all study materials (completed, partially completed, and blank eCRFs, study drug, etc.) must be returned to CARA. Study drug must be destroyed at the site authorized by CARA or returned to the Sponsor.

14. REFERENCES

1. Investigator's Brochure for CR845. Edition No. 2, Release date: 11 April 2014, Cara Therapeutics, Inc.
2. Farrar JT, Young JP, La Moreaux L, Werth JL, and Poole MR: Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain.* (2001); 94:149-158.
3. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to anti-rheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol*. 1988; 15:1833-1840.
4. Bellamy N. Pain assessment in osteoarthritis: experience with the WOMAC osteoarthritis index. *Semin Arthritis Rheum*. 1989; 18:14-17.
5. Smith, HS, Smith JM, Seidner. Opioid-induced nausea and vomiting. *Annals of Palliative Medicine*. July 2012.
6. Cui L, Hung HM, Wang SJ. Modification of sample size in group sequential clinical trials. *Biometrics*. September 1999; 55:853-857.

15. SCHEDULE OF EVENTS

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
	Day -14 to Day -1	Day 1	Day 8	Day 15	Day 22	Day 29	Day 43	Day 57	Follow-Up Visit
Study Procedure	***Screening***	***Baseline***	***Titration to Effect Period***				***Maintenance Treatment Period***		***Follow-Up Period***
Informed consent	X								
Inclusion/exclusion criteria	X	X							
Medical history, demographics, and identify index joint	X								
Record prior medications[1]	X	X							
Height and weight	X								
Drug screening test	X								
Training on PRO completion [2]	X								
Training on Patient Diary Completion [3]	X								
Provide acetaminophen [4]	X	X	X	X	X	X	X		
Discontinue current pain[5] medications	X[5]								
	Screening	***Baseline***	***Titration to Effect Period***				***Treatment Period***		***Follow-Up***
Assign to treatment [6]		X							
Review PRO and Patient Diary completion [2,3]		X	X	X	X	X	X	X	
Drug accountability		X	X	X	X	X	X	X	X
Instruct on fluid replacement		X	X	X	X	X	X		
Dispense study drug [7]		X	X	X	X	X	X		
Record concomitant medications[8]	X	X	X	X	X	X	X	X	
Review of information and titration determination and enter into IWRS			X	X	X	X			

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
	Day -14 to Day -1	Day 1	Day 8	Day 15	Day 22	Day 29	Day 43	Day 57	Follow-Up Visit
Safety	***Screening***	***Baseline***	***Titration to Effect Period***				***Treatment Period***		***Follow-Up***
Physical examination [9]	X							X	
Vital signs [10]	X	X	X	X	X	X	X	X	X
12-lead ECG	X							X	
Pregnancy test [11]	X	X							
Clinical laboratory evaluations [12]	X	X						X	
Serum sodium measurement [13]	X	X	X	X	X	X	X	X	
Adverse event assessment		X	X	X	X	X	X	X	X
Effectiveness	***Screening***	***Baseline***	***Titration to Effect Period***				***Treatment Period***		***Follow-Up***
Daily joint pain (NRS) [14]	X	X	X	X	X	X	X	X	
WOMAC Index [15]		X	X	X	X	X	X	X	
Patient Global Assessment of OA[16]								X	

1. *Prior Medications:* Prior medications are defined as medications taken at any time during the 30 days prior to Screening until the time of dosing on Day 1, whether continuing or not. Any changes to prior medications (dose, regimen, etc.) during the course of the study must be considered as a new concomitant medication.
2. *Patient-reported Outcome Training:* A member of the clinical staff will review the patient-reported outcome assessments for this study with each patient during the Screening and Baseline Visits. Patient-reported outcome assessments for this study are the Numeric Rating Scale, the Western Ontario and McMaster Osteoarthritis Index, and the Patient Global Impression of Change
3. *Patient Diary:* Patients will be shown how to capture their daily pain scores and the number of rescue medication tablets taken each day (the preceding 24 hours) in their diaries beginning 7 days before their scheduled Baseline Visit and continuing for the duration of the Titration-to-Effect and Maintenance Treatment Periods.
4. *Rescue Medication:* A bottle of analgesic rescue medication (acetaminophen, 325 mg) will be provided at the Screening Visit to be used (if needed) throughout the study. Patients will be instructed to take acetaminophen as needed for pain (up to 2 tablets of 325mg per administration for a maximum of 8 tablets per day). Patients will also be instructed to bring the bottle of medication back with them for each clinic visit for drug accountability and dispensation of another bottle of rescue medication if needed. Patients should also be instructed not to take any analgesic rescue medication within 12 hours of a scheduled clinic visit to prevent confounding of the pain assessments during the visit.

5. *Discontinuation of Pain Medication:* Patients will be instructed to discontinue their current nonsteroidal anti-inflammatory drugs and opioid analgesic medications starting on Day -5 and continuing for the duration of the study (through Day 57).
6. *Treatment Assignment:* Patients will be enrolled and assigned to treatment following successful completion of the Baseline assessments.
7. *Dispensing of Study Medication:* Study medication will be dispensed to patients in bottles of 15 tablets at the Baseline Visit. The patients will take their first dose of study medication at the clinic.
8. *Concomitant Medications:* Concomitant medications are defined as medications taken at any time from post-dose on Day 1 until the end of the study (i.e., at the Follow-up Visit). Any new concomitant medication added during the Titration-to-Effect and Maintenance Treatment Periods must also have the reason for taking the new concomitant medication recorded in the case report form. Any concomitant medication administered due to an adverse event must also be recorded on the adverse event case report form page.
9. *Physical Exam:* A physical examination will be performed at Screening and on Day 57 (or early termination). On Day 57, any changes from the previous physical exam conducted at Screening will be noted.
10. *Vital Signs:* Vital signs will be measured at each clinic visit. Vital signs (blood pressure and heart rate) at the Screening visit will be conducted in both the supine and standing positions. For the purpose of these assessments, patients should be assessed in the supine position first and then, after sitting up for at least 1 minute, should be standing for at least 3 minutes prior to measuring blood pressure or heart rate. For the remainder of the study, vital signs will be assessed in the sitting position. Body temperature will be measured at screening and at Day 57 (or early termination).
11. *Pregnancy Testing:* For female patients of childbearing potential, a serum pregnancy test will be conducted at Screening and a urine pregnancy test will be conducted at the Baseline Visit prior to the administration of study drug. "Childbearing potential" is defined in Section 7.6.
12. *Laboratory Evaluations:* Clinical laboratory evaluations will consist of hematology and blood chemistry and will be conducted at Screening, at Baseline (prior to drug administration), and on Day 57 (or early termination).
13. *Serum Sodium Measurement:* Blood samples to measure serum sodium levels will be taken at all visits (or early termination). If at any time during the study, the patient's serum sodium level is > 150 mmol/L, dosing should be paused for patient assessment (i.e., retesting of sodium in approximately 1 hour after the patient is given a glass of water and clinical evaluation). Based upon the outcome of the clinical evaluation by the clinical staff, the dosing of study medication will either be: a) continued or b) terminated.
14. *Daily Joint Pain:* The average daily index joint pain intensity will be assessed using the numeric rating scale. The numeric rating scale score will be recorded into the electronic case report form by the site at the Screening Visit and by the patient each day (at approximately 6:00 PM) in their patient diary. The patient should make all attempts to assess their joint pain at the same time each day. During the Screening Period, assessments will be conducted for 5 days prior to the Baseline Visit.
15. The Western Ontario will be completed at each clinic visit from Baseline to Day 57 (or early termination).
16. The Patient Global Impression of Change will be completed on Day 57 (or early termination).

    A visit window of +/- 1 day will be allowed

16. APPENDICES

Appendix 1 Regulations and Guidelines

a) Declaration of Helsinki

This Policy of the World Medical Association is available at URL:

http://www.wma.net/en/30publications/10policies/b3/index.html

Approval by an Institutional Review Board

For IND studies, the minimum standards of conduct and requirements for informed consent are defined in the FDA regulations.

This protocol must be reviewed and approved by a valid IRB before initiation of the study. Written notification of approval is to be submitted by the Investigator to the CARA, Inc. monitor before shipment of investigational drug supplies, and will include the date of the committee's approval and the chairperson's signature. This written approval must consist of a completed CARA, Inc. IRB Approval form or written documentation from the IRB containing the same information.

Until written approval by the IRB has been received by the Investigator, no patient may undergo any procedure solely for determining eligibility for this study.

Protocol amendments must also be reviewed and approved by the IRB. Written approval from the IRB, or a designee, must be received by CARA, Inc., before implementation. This written approval will consist of a completed IRB Approval form or written documentation from the IRB containing the same information.

b) FDA Regulations

Refer to the following United States Code of Federal Regulations (CFR):

- FDA Regulations 21 CFR
  Parts 50.20 - 50.27
  Subpart B - Informed Consent of Human Patients
- FDA Regulations 21 CFR Parts 56.107 - 56.115
  Part 56-Institutional Review Boards
  Subpart B - Organization and Personnel
  Subpart C – IRB Functions and Operations
  Subpart D – Records and Reports
- FDA Regulations 21 CFR Parts 312.50 - 312.70
  Subpart D - Responsibilities of Sponsors and Investigators

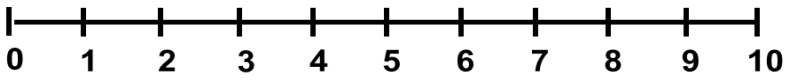
Appendix 2 Numerical Rating Scale

This is a sample of the Numerical Rating Scale.

Instructions: Show the pain scale to the patient and explain that on the 0 to 10 pain rating scale, 0 means no pain and 10 means the worst possible pain. A value in the middle of the scale (around 5) would be moderate pain; a value of 2 or 3 would be mild pain, and a value of 7 or higher is considered severe pain.

Ask the patient the following question: "On a scale of 0 – 10, with 0 being 'no pain' and 10 being the 'worst possible pain', how would you rate your average pain *in the last 24 hours*?"

The intent of the question is to gain an understanding of the intensity of the patient's index joint pain.



No Pain **Worst Possible Pain**

Adapted from: Farrar JT, Young JP, La Moreaux L, Werth JL, and Poole MR: Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 94 (2001) 149–158.

Appendix 3 Western Ontario and McMaster Osteoarthritis Index

This is a sample questionnaire. The actual questionnaire will be provided in the eCRF.

Patients will be provided with the Western Ontario and McMaster Osteoarthritis Index (WOMAC) scale and instruction sheet at each clinic visit at which the patient is scheduled to be assessed using the WOMAC questionnaire.

The WOMAC index is used to assess patients with osteoarthritis of the hip or knee using 24 parameters. It can be used to monitor the course of the disease or to determine the effectiveness of anti-rheumatic medications. Additional information regarding this scale can be found in the WOMAC Osteoarthritis Index Guide that will be provided to the sites.

Patients will be asked to score the impact of their index joint OA on each of the parameters for pain, stiffness and activities (function) using the 11-point numerical scales shown below.

Patients should put an "X" in the box that best represents their score for that item. The time frame of assessment is the past 48 hours.

Pain:

1. Walking on a flat surface
2. Stair climbing
3. Nocturnal (at night, lying in bed)
4. Rest (sitting or lying down)
5. Weight bearing (standing upright)

No Pain	0	1	2	3	4	5	6	7	8	9	10	Extreme Pain

Stiffness:

1. Morning stiffness
2. Stiffness occurring later in the day

No Stiffness	0	1	2	3	4	5	6	7	8	9	10	Extreme Stiffness

Function

1. Difficulty descending stairs
2. Difficulty ascending stairs
3. Rising from sitting
4. Standing
5. Bending to floor (to pick something up)
6. Walking on a flat surface
7. Getting in or out of car
8. Going shopping
9. Putting on socks
10. Rising from bed
11. Taking off socks
12. Lying in bed
13. Getting in and out of the bathtub
14. Difficulty sitting (for a period of time)
15. Getting on or off the toilet
16. Heavy domestic duties
17. Light domestic duties

No Difficulty	0	1	2	3	4	5	6	7	8	9	10	Extreme Difficulty

Appendix 4 Patient Global Impression of Change

This is a sample questionnaire.

The patients will provide their overall impression of the status of their OA in the index joint on a 7-point scale where 1 = “Very much improved” and 7 = “Very much worse.”

Patients will be asked to complete the following statement: “Since the start of the study, my osteoarthritis is?” The response options are as follows:

1. Very much improved
2. Much improved
3. Minimally improved
4. No change
5. Minimally worse
6. Much worse
7. Very much worse

Appendix 5 Investigator Approval Statement

A Randomized, Double-Blind, Placebo-Controlled, Titration-to-Effect Study of Orally Administered CR845 in Patients with Osteoarthritis of the Hip or Knee

Protocol: CR845-CLIN2002-PO

I have read and understand the protocol (CR845-CLIN2002-PO) and the Investigator's Brochure and I agree that these documents contain all the information necessary to conduct this study. I will conduct the study as outlined in the protocol and any amendment(s) to the protocol.

In my formal capacity as Investigator, I understand the study protocol and will conduct this study according to the principles of Good Clinical Practice (in compliance with the International Conference on Harmonisation Harmonized Tripartite Guideline for Good Clinical Practice E6 dated 10 June 1996) and all applicable federal and local regulations.

I will ensure that all individuals assisting with the study are adequately trained and informed about the protocol, investigational product(s), procedures and they study-related duties and functions.

I agree not to deviate from the protocol without prior agreement from the Sponsor except to avoid an immediate safety hazard to the study subjects.

I further agree that the Sponsor, Sponsor designees, and federal agencies shall have access to all source documents and records associated with the study for review and monitoring of the investigational trial.

Printed Name: Principal Investigator _____

Signature: _____

Title: _____

Study Site/Site Number: _____

Date: _____