AN OPEN-LABEL, MULTICENTER, EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY OF INTRAVENOUS CR845 IN HEMODIALYSIS PATIENTS WITH CHRONIC KIDNEY DISEASE-ASSOCIATED PRURITUS

Protocol number:	CR845-CLIN3101
Phase:	3
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Sponsor:	Cara Therapeutics, Inc. 4 Stamford Plaza Stamford, CT 06902 (203) 406-3700

SPONSOR APPROVAL / SIGNATURE PAGE

Medical Monitor Name and Contact Information

Refer to the Investigator Site File (ISF).

INVESTIGATOR APPROVAL STATEMENT

I have read and understand the protocol (CR845-CLIN3101) and I agree that this document contains all ethical, legal, and scientific information necessary to conduct this study. I will oversee the conduct of the study as described in the protocol and any amendment(s) made to the protocol.

I agree to conduct the study as detailed herein and in compliance with the current International Council for Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice E6 (R1) and United States Code Title 21 (Food and Drug Administration), and applicable regulatory requirements.

Principal Investigator (refer to Investigator Site File [ISF])

Printed Name: _____

Signature: _____

Date: _____

1.0 Protocol Synopsis

STUDY TITLE	An Open-Label, Multicenter, Extension Study to Evaluate the Long-Term Safety of Intravenous CR845 in Hemodialysis Patients with Chronic Kidney Disease-Associated Pruritus
PROTOCOL NUMBER	CR845-CLIN3101
PHASE OF DEVELOPMENT	3
INVESTIGATIONAL PRODUCT	CR845 Solution
NAME OF ACTIVE INGREDIENT	CR845
ROUTE OF ADMINISTRATION	Intravenous (IV)
STUDY CENTERS	Sites in the United States that were part of the Phase 2 clinical studies CR845-CLIN2005 (Part B) or CR845-CLIN2101 (Part A), and up to 20 additional sites that were not part of the Phase 2 clinical studies CR845-CLIN2005 (Part B) or CR845-CLIN2101 (Part A).
OBJECTIVES	To evaluate the safety of IV CR845 at a dose of 0.5 mcg/kg administered after each dialysis session over a Treatment Period of up to 52 weeks in hemodialysis patients who previously participated in the Phase 2 studies CR845-CLIN2005 (Part B) or CR845-CLIN2101 (Part A) and in hemodialysis patients who had not been previously exposed to CR845 and did not previously participate in the Phase 2 studies CR845-CLIN2005 (Part B) or CR845-CLIN2101 (Part A) (de novo patients).
NUMBER OF PATIENTS	Approximately 300
STUDY POPULATION	**Inclusion Criteria:** To be eligible for inclusion into the study, a patient must meet the following criteria: 1. Willing and able to provide written informed consent prior to participating in this study; 2. Able to communicate clearly with the Investigator and staff, able to understand the study procedures, and able and willing to comply with the study schedules and all study requirements; 3. Males or females 18 years of age or older who participated in either CR845-CLIN2005 (Part B) or CR845-CLIN2101 (Part A) or de novo patients; 4. Currently on hemodialysis for end-stage renal disease and has been categorized as experiencing moderate to severe uremic pruritus as part of CR845-CLIN2005 (Part B) or CR845-CLIN2101 (Part A); or de novo patients

	5. Continues to experience chronic kidney disease-associated pruritus since the previous study (ie, CR845-CLIN2005 [Part B] or CR845-CLIN2101 [Part A]); de novo patients experiencing chronic kidney disease-associated pruritus at the time of Screening 6. If female: a. Is not of childbearing potential (surgically sterile or postmenopausal, as defined in Section 6.5.1.6); or b. Has a negative serum pregnancy test at screening and agrees to use acceptable contraceptive measures (as defined in Section 6.5.1.6) from the time of informed consent until the safety Follow-up Visit or 7 days after the last dose of study drug, whichever is later. 7. If male, agrees not to donate sperm after the first dose of study drug until 7 days after the last dose, and agrees to use a condom with spermicide or abstain from heterosexual intercourse during the study until 7 days after study drug administration. (Note: No restrictions are required for a vasectomized male provided his vasectomy was performed ≥4 months prior to dosing); 8. Has a dry body weight of ≥40.0 kg at screening (prescription target dry body weight); 9. Has adequacy of dialysis, defined as meeting 1 of the following criteria during the 3 months prior to screening: a. ≥2 single-pool Kt/V measurements ≥1.2; or b. ≥2 urea reduction ratio measurements ≥65%; or c. 1 single-pool Kt/V measurement ≥1.2 and 1 urea reduction ratio measurement ≥65% 10. For de novo patients only, has recorded up to 4 Worst Itching Intensity NRS scores at dialysis visits over the week prior to the first dose (including the score on Day 1 of dosing), and has at least 1 of the NRS scores >4.

	Exclusion Criteria: A patient will be excluded from the study if any of the following criteria are met: 1. Received an investigational drug (other than study drug received while participating in CR845-CLIN2005 [Part B] or CR845-CLIN2101 [Part A]) within 30 days prior to the first dose of study drug, or is planning to participate in another interventional clinical study while enrolled in this study. 2. Has a concomitant disease or any medical condition that, in the opinion of the Investigator, could pose undue risk to the patient, impede completion of the study procedures, or would compromise the validity of the study measurements, including, but not limited to: a. Known or suspected history of Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, - diagnosed alcohol, narcotic or other drug abuse, or substance dependence within 12 months prior to screening; b. New York Heart Association Class IV congestive heart failure (Appendix 1, Section 14.0); c. Severe mental illness or cognitive impairment (eg, dementia); d. Any other relevant acute or chronic medical or neuropsychiatric condition; 3. Abnormal liver function, defined as: a. Serum alanine aminotransferase or aspartate aminotransferase >2.5 times the reference upper limit of normal (ULN) at screening; and/or b. Total bilirubin >2 times ULN at screening. **De novo patients will be excluded if any of the following criteria are met at the time of entry into the study:** 4. Known history of allergic reaction to opiates, such as hives or anaphylaxis (Note: side effects related to the use of opioids, such as constipation or nausea, would not exclude patients from the study). 5. In the opinion of the Investigator, has pruritus attributed to a cause other than ESRD or its complications (eg, patients with concomitant pruritic dermatological disease or cholestatic liver disease) (Note: Patients whose pruritus is attributed to ESRD complications, such as hyperparathyroidism, hyperphosphatemia, anemia, or the dialysis procedure or prescription may be enrolled); 6. Has localized itch restricted to the palms of the hands;

STUDY DESIGN	This is an open-label multicenter, long-term extension safety study to evaluate the safety of IV CR845 administered after each dialysis session over a Treatment Period of up to 52 weeks. Patients who have participated in CR845-CLIN2005 (Part B) or CR845-CLIN2101 (Part A) may participate in this single-group study, as may patients who had not been previously exposed to CR845 and did not participate in CR845-CLIN2005 (Part B) or CR845-CLIN2101 (Part A) (de novo patients). This study will consist of a Screening Visit, a 52-week Treatment Period, and a Follow-up Visit. Informed consent will be obtained prior to performing any study-specific procedures. All patients will have a Screening Visit, which can be performed anytime within 14 days prior to the first dose of study drug, to confirm eligibility. De novo patients must have at least 1 Worst Itching Intensity NRS score >4 recorded during the Screening Period (Day -7 to Day 1) to be eligible. Day 1 of the Treatment Period will be defined as the day of administration of the first dose of study drug. Each patient will receive CR845 at a dose of 0.5 mcg/kg after each dialysis session, 3 times per week for up to 52 weeks. All scheduled study visits during the Treatment Period will be conducted on dialysis days. Clinical laboratory tests, electrocardiograms (ECGs), vital signs, adverse events, and concomitant medications will be monitored throughout the study. Blood samples for inflammatory biomarkers will be collected from all patients prior to dialysis on Day 1 and periodically until the End of Treatment or Early Termination Visit. Blood samples will also be collected periodically for clinical laboratory tests. The number and reason(s) for missed dialysis will be recorded throughout the study. Incidence of infection and use of antibiotics, hospitalizations, emergency department encounters (EDE) or observation stays (OBS)will also be recorded as applicable. Use of antipruritic medications, iron and erythropoiesis-stimulating agent (ESA) will be recorded throughout the study. The last dose of study drug will be administered at the last dialysis visit on Week 52, or early termination. The End of Treatment Visit will be conducted at the dialysis visit following the last dose. A final safety Follow-up Visit will be conducted 7 to 10 days after the End of Treatment or Early Termination Visit.
STUDY DRUG	CR845 at a concentration of 0.05 mg/mL (single-use vial)
REFERENCE PRODUCT	No placebo will be used for this study.
TREATMENT REGIMENS	Patients will be administered 0.5 mcg/kg CR845 as a single IV bolus 3 times a week after each dialysis session for up to 52 weeks.

STUDY DURATION	Screening Visit: up to 14 days Treatment Period: up to 52 weeks End of Treatment Visit: on Week 53 or at early termination Follow-up Visit: 7-10 days after the End of Treatment Visit (Week 54 or Week 55), or Early Termination Visit Total study duration for a single patient: up to approximately 57 weeks
STUDY ASSESSMENTS	Safety Assessments: The safety assessments used to evaluate the overall safety of CR845 will include the seriousness, severity and relationship to study drug of adverse events; vital signs; 12-lead ECGs; and clinical laboratory evaluations. Other Assessments: Other assessments will include missed dialysis due to adverse event/serious adverse event, incidence of infection and use of antibiotics, hospitalization and/or EDE and OBS, use of antipruritic medications, levels of inflammatory biomarkers, changes in iron status, and use of ESAs measured at various time throughout the Treatment Period.
INTERIM ASSESSMENT	There will be no interim assessment performed in this study.
STATISTICAL ANALYSIS	The Safety Population is defined as all patients who received at least 1 dose of CR845 in this study. Safety data will be summarized descriptively. No inferential statistics are planned. Adverse event data will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT), and will include summaries of treatment-emergent adverse events, serious adverse events, deaths and adverse events resulting in study drug discontinuation. Vital signs, clinical laboratory results, and ECG data will be descriptively summarized by visit, as applicable, in addition to change from baseline. Analyses will also be conducted for missed dialysis, incidence of infection and use of antibiotics, incidence of hospitalization and/or EDE and OBS, use of iron and ESA, use of antipruritic agents, and levels of inflammatory biomarkers.

2.0 Table of Contents

LIST OF TABLES

LIST OF FIGURES

3.0 List of Abbreviations

ATC	Anatomical Therapeutic Chemical
CI	confidence interval
CFR	Code of Federal Regulations
CNS	central nervous system
de novo	Patients who were not part of the Phase 2 clinical studies CR845-CLIN2005 (Part B) or CR845-CLIN2101 (Part A) (de novo patients) and have not been previously exposed to CR845
DMC	Data Monitoring Committee
ECG	electrocardiogram
EDE	emergency department encounter(s)
eCRF	electronic case report form
ESA	erythropoiesis-stimulating agent
FDA	Food and Drug Administration
GCP	Good Clinical Practice
H	above laboratory reference range
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IL	interleukin
IND	Investigational New Drug
IRB	Institutional Review Board
ISF	Investigator Site File
IV	intravenous
KOR	kappa-opioid receptor
L	below laboratory reference range
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
MOR	mu-opioid receptor
N	within laboratory reference range
NRS	numerical rating scale
OBS	observation stay(s)
PK	pharmacokinetic(s)
PT	Preferred Term
SAE	serious adverse event
SAP	statistical analysis plan
SOC	System Organ Class
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WHO-DD	World Health Organization Drug Dictionary

4.0 Introduction

4.1 Background and Rationale

CR845 is a kappa-opioid receptor (KOR) agonist with a peripheral mechanism of action being developed by Cara Therapeutics, Inc. (designated as Cara Therapeutics or Sponsor in this protocol) as a novel therapeutic agent for the symptomatic relief of acute and chronic pain and pruritus.

Opioid receptors are involved in the modulation of itch and 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 tissues, such as skin and viscera, and in the immune system (see Investigator's Brochure for references and further details). An opioid analgesic like morphine acts primarily via activation of the mu-opioid receptor (MOR) located in the CNS and peripheral nervous system, and as such, is associated with a wide array of side effects, including sedation, respiratory depression, abuse liability, and constipation. CR845 was designed to activate KORs located primarily in the peripheral nervous system, which are known to modulate itch, pain, and inflammatory signals without producing the side effects associated with the activation of MORs.

CR845 is a potent and selective KOR agonist with more than 30,000-fold selectivity over mu- and delta-opioid receptors and does not demonstrate activity at other receptors, ion channels, or transporters. CR845's unique peptidic structure significantly differs from other small molecule KOR agonists developed to date, which, for the most part, are CNS-active. Being a hydrophilic peptide, CR845 has limited membrane permeability by passive diffusion, which limits its access to the CNS. Thus, the compound preferentially activates KORs located outside the CNS.

Based on nonclinical pharmacological studies, it is anticipated that CR845 will produce a combined analgesic, anti-itch, and anti-inflammatory effect (see Investigator's Brochure for details).

Uremic pruritus is a highly prevalent complication of chronic kidney disease, present in many patients undergoing dialysis treatment [Pisoni 2006]. Most patients affected by pruritus will continue to experience the symptoms for months or years [Mathur 2010], with current antipruritic treatment unable to provide adequate relief, resulting in the unremitting nature of the symptoms.

Although an association between chronic renal failure and skin itching has been recognized for many years, the etiology and pathophysiology of uremic pruritus has not been completely elucidated. It is likely to be multifactorial and include abnormalities related to uremia, such as those involving calcium and phosphorus. It has also been postulated to involve immune system dysfunction, opioid dysregulation, iron deficiency anemia, and neuropathic changes [Pisoni 2006; Wang 2010]. Recent research has focused on systemic and dermal microinflammation as well as on the hypothesis that uremic pruritus is a result of an imbalance between the activation of MORs and KORs [Kimmel 2006; Narita 2006; Phan 2012; Patel 2007]. In support of the inflammatory

hypothesis, there is evidence that many hemodialysis patients have elevated cytokines (such as interleukin-6 levels), and hemodialysis patients with pruritus have increased T helper type 1 cells and C-reactive protein [Kimmel 2006; Patel 2007]. Furthermore, immunomodulators that decrease the production of pro-inflammatory cytokines have been shown to reduce pruritus [Mettang 2002; Tey 2011].

4.2 Clinical Experience

4.2.1 Overall Exposure

To date, the intravenous (IV) formulation of CR845 has been evaluated in approximately 700 patients and healthy volunteers across 7 Phase 1 studies (including 2 studies conducted in Japan), 3 Phase 2 studies for the relief of moderate-to-severe, acute postoperative pain, and 2 Phase 2 studies for the relief of moderate-to-severe pruritus in hemodialysis patients. CR845 has been evaluated both as an IV bolus and a 15-minute infusion of single or repeated doses ranging from 0.5 to 40 mcg/kg.

Of the patients exposed to IV CR845 to date, 213 hemodialysis patients (127 males and 86 females) have received single or repeated IV injections of CR845 doses (for up to 8 weeks) ranging from 0.5 to 6 mcg/kg across 2 Phase 1 studies and 2 Phase 2 safety and efficacy studies.

4.2.2 Safety in Hemodialysis Patients

A review of the aggregate safety data shows that CR845 was safe and well tolerated in a complex population of hemodialysis patients with multiple comorbidities when administered after each dialysis session for up to 8 weeks at IV doses ranging from 0.5 mcg/kg to 6 mcg/kg. Although patients exposed to CR845 reported more adverse events compared with placebo patients, most events were mild or moderate in nature. Generally mild, transient paresthesias (facial tingling) and/or hypoesthesias (in different anatomic locations), mostly on the first week of dosing, as well as headache, dizziness, and somnolence, were the most frequently reported adverse events associated with CR845 administration. Of note, psychiatric side effects (eg, dysphoria and hallucinations) commonly associated with centrally-acting kappa opioids were not reported in patients exposed to CR845. Consistent with its lack of affinity for MORs, CR845 did not cause euphoria, respiratory depression, or reduction in oxygen saturation.

CR845-CLIN2101 (Part A) evaluated the safety, pharmacokinetics (PK), and efficacy of repeated IV doses of CR845 compared to placebo over an 8-week treatment period in 174 hemodialysis patients. This study is the longest treatment period evaluated to date in hemodialysis patients and no clinically important or significant safety findings related to CR845 were noted. As expected with patients on hemodialysis, a significant number of serious adverse events (SAEs) were reported that were considered not related to study drug. A total of 34 of the 174 patients (19.5%) randomized and treated in the study experienced SAEs. Only 1 SAE was considered probably related to study drug by the Investigator for an episode of mental status changes (moderate in severity), although

based on medical review by the Sponsor, it was deemed that an alternate etiology of urgent/emergent hypertension may have resulted in the acute change in mental status. There were 4 patient deaths during the conduct of the study, all of which were considered not related to the study drug.

In patients with normal renal function, CR845 can cause free-water diuresis (aquaresis) and increased serum sodium. However, as would be expected in patients undergoing dialysis in whom there are few functioning nephrons, there was no evidence of aquaresis or significant increases in serum sodium concentrations. There were no adverse trends in clinical chemistry or hematology values (drawn pre-dialysis), including, as noted, no apparent differences between the placebo and CR845 groups in serum sodium. There were no discernable differences between treatment groups in vital sign results. Of particular note, among patients receiving CR845, there was no apparent reduction in blood pressure or respiratory rate following dosing, in contrast to the expected effects of MOR agonists.

Adverse event summary tables can be found in the Investigator's Brochure, with further details of the safety profile of CR845.

4.2.3 Efficacy of CR845 in Hemodialysis Patients with Uremic Pruritus

The efficacy of CR845 in uremic pruritus was evaluated in 2 Phase 2, randomized, double-blind, placebo-controlled studies (CR845-CLIN2005 [Part B] and CR845-CLIN2101 [Part A]).

CR845-CLIN2005 (Part B) included 65 hemodialysis patients with moderate-to-severe uremic pruritus who received either IV CR845 1.0 mcg/kg (n=33) or placebo (n=32) 3 times per week for 2 weeks, after each hemodialysis session during that time period. CR845 significantly decreased itching intensity (P=0.016 versus placebo) and significantly improved quality of life related to itching (Skindex-10 Scale) (see Investigator's Brochure for details). Furthermore, CR845-treated patients exhibited statistically significant reductions in both daytime (P=0.03) and nighttime (P=0.007) worst itching scores compared with placebo, and the reduction in itching intensity scores was similar on dialysis and nondialysis days. The separation of CR845-treated patients from placebo-treated patients in itching intensity was evident by Day 3 of treatment and continued to increase into Week 2.

CR845-CLIN2101 (Part A) evaluated the safety, pharmacokinetics (PK), and efficacy of repeated IV doses of CR845 compared to placebo over an 8-week treatment period in 174 hemodialysis patients experiencing moderate-to-severe uremic pruritus daily or near-daily for 4.4 years on average. The study took placed at 33 dialysis centers and assessed the effect of 3 doses of CR845 (ie, 0.5 mcg/kg, n=44; 1 mcg/kg, n=41 and 1.5 mcg/kg, n=44) or placebo (n=45) administered at the end of each dialysis session (ie, 3 times/week). The primary efficacy endpoint for Study CR845-CLIN2101 (Part A) was based on itch intensity measurement and defined as the change from a 1-week baseline recorded prior to the start of study drug to the last week of the 8-week treatment period with respect to the weekly mean of the daily 24-hour Worst Itching Intensity numerical

rating scale (NRS) score. The least squares (LS) mean (±SE) treatment group difference from placebo at Week 8 across all CR845 doses was -1.3 (±0.41) (95% confidence interval [CI]: -2.1 to -0.5) (P=0.002) with an average NRS score reduction from baseline of -3.2 (±0.22) (LS mean ± SE) and 95% CI ranging from -3.7 to -2.8. Examination of the individual CR845 dose group results for the Full Analysis Population indicates that a substantial improvement over placebo was observed with all 3 doses. These differences from placebo were statistically significant for the lower dose group of 0.5 mcg/kg (P<0.001) and the 1.5 mcg/kg group (P=0.019), with an effect size estimated as 0.82, 0.39, and 0.62 for the 0.5, 1.0, and 1.5 mcg/kg doses, respectively. Average reduction from baseline (LS mean ± SE) ranged from -2.8 (±0.38) in the 1.0 mcg/kg dose group (95% CI ranging from -3.5 to -2.0) to -3.8 (±0.38) in the 0.5 mcg/kg dose group (95% CI ranging from -4.5 to -3.1).

4.2.4 Pharmacokinetics in Hemodialysis Patients

CR845 is eliminated primarily through the kidney and no major metabolites have been identified in humans. Consequently, total body clearance of CR845 in patients with severe renal impairment is reduced relative to healthy, matched, control subjects (CR845-CLIN1005) such that plasma levels of CR845 remain relatively constant until cleared during dialysis in hemodialysis patients (CR845-CLIN1003 and CR845-CLIN2005 [Part A]). Half-life ranges between 18 to 24 hours in hemodialysis patients compared to a typical range of 2 to 3 hours in subjects with normal renal function. Thus, lower doses of CR845 can be administered at a less frequent interval in hemodialysis patients to achieve the same or higher overall exposure compared to individuals with normal renal function. Based on this PK profile, CR845 does not need to be administered more than 3 times a week after each hemodialysis session, which is convenient for this patient population and ensures treatment compliance in a population already burdened with complex medication schedules.

The PK profile of repeat-dose CR845 was studied in 24 hemodialysis patients who received doses of 0.5, 1.0, or 2.5 mcg/kg 3 times per week for 1 week (CR845-CLIN2005 [Part A]). In this study, there were dose-proportional increases in maximum concentration and area under the curve, and minimum to no accumulation with repeat doses due to clearance of the drug by hemodialysis (see Investigator's Brochure for details).

4.3 Summary of Potential Risks and Benefits

During preclinical development, there were no specific safety findings to preclude the use of CR845 in humans. During early clinical development, IV CR845 was administered to healthy volunteers; patients with mild, moderate, or severe renal impairment, including end-stage renal disease (ESRD) and hemodialysis patients; recreational poly-drug users;

and postsurgical patients. The effects of CR845 have been shown to be in line with the underlying pharmacological mechanism of KOR activity. Consistent with the nonclinical abuse liability studies conducted to date, the results of an abuse-potential study in humans indicated that CR845 appears to present a low risk for abuse potential in humans in comparison to currently clinically used opioids.

While it has been demonstrated that CR845 has substantially less access to the CNS than previously tested kappa agonists, nervous system effects, mostly nonserious adverse events, have been reported in CR845-treated subjects. Adverse events related to aquaresis (such as elevated serum sodium and tachycardia) have been observed in subjects with normal renal function but has not been observed in patients with chronic-kidney disease.

Overall, tingling/numbness, dizziness, fatigue and/or drowsiness/somnolence were the most common adverse events. Precaution is recommended in the operation of machinery for patients who experience dizziness, fatigue, and/or drowsiness/somnolence. This is described in the informed consent form (ICF), as appropriate, and should be discussed with each patient prior to initiation of the study. In general, CR845 appeared to be safe in both single- and repeat-dose clinical studies, which support continued study and development of this compound.

5.0 Objectives

The objective of this study is to evaluate the safety of IV CR845 at a dose of 0.5 mcg/kg administered after each dialysis session over a Treatment Period of up to 52 weeks in hemodialysis patients who previously participated in the Phase 2 studies CR845-CLIN2005 (Part B) or CR845-CLIN2101 (Part A) and in de novo hemodialysis patients who had not been previously exposed to CR845 and did not previously participate in the Phase 2 studies CR845-CLIN2005 (Part B) or CR845-CLIN2101 (Part A).

6.0 Investigational Plan

6.1 Overall Study Design and Plan: Description

This is a multicenter, open-label, Phase 3 study to evaluate the long-term safety of IV CR845, administered for up to 52 weeks after each dialysis session to patients who participated in CR845-CLIN2005 (Part B) or CR845-CLIN2101 (Part A), and de novo hemodialysis patients who had not been previously exposed to CR845 and were not part of the Phase 2 clinical studies CR845-CLIN2005 (Part B) or CR845-CLIN2101 (Part A). This study will consist of a Screening Visit, a 52-week study drug Dosing Period, an End of Treatment Visit, and a Follow-up Visit. Informed consent will be obtained prior to performing any study-specific procedures. All patients will have a Screening Visit, which can be performed anytime within 14 days prior to the first dose of study drug, to confirm eligibility.

It will be necessary to confirm that de novo patients have moderate-to-severe pruritus as measured by the 24-hour Worst Itching Intensity numerical rating scale (NRS). NRS scores will be collected at each dialysis visit in the week prior to the first dose (including the score on Day 1 of dosing). To be eligible for participation, at least 1 NRS score must be >4. These criteria for eligibility should not be communicated to the patients.

Day 1 of the Treatment Period will be defined as the day of administration of the first dose of study drug. Each patient will receive CR845 at a dose of 0.5 mcg/kg after each dialysis session, 3 times per week for up to 52 weeks, as indicated in Section 6.4.5. The duration of the study drug dosing for each individual patient is expected to be up to 52 weeks for a total of approximately 156 doses of study drug (generally 3 doses per week). All scheduled study visits during the Treatment Period will be conducted on dialysis days.

Clinical laboratory tests, electrocardiograms (ECGs), vital signs, adverse events, and concomitant medications will be monitored throughout the study. Blood samples for inflammatory biomarkers will be collected from all patients prior to dialysis on Day 1 and periodically until the End of Treatment or Early Termination Visit, per the schedule of events (Table 1). Blood samples will also be collected periodically for clinical laboratory tests.

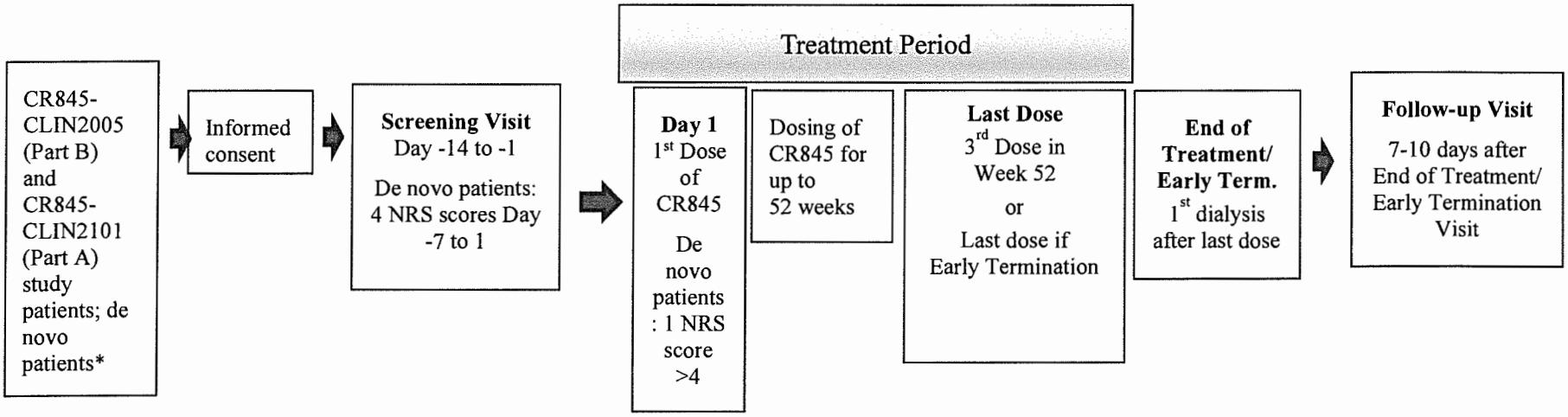
The number and reason(s) for missed dialysis will be recorded throughout the study. Incidence of infection, hospitalizations, emergency department encounters (EDE) or observation stays (OBS), and/or use of antibiotics will also be recorded with reason for infection, if available. Iron and erythropoiesis-stimulating agent (ESA) use will be recorded throughout the study.

The last dose of study drug will be administered at the last dialysis visit on Week 52, or early termination. The End of Treatment visit will be conducted at the dialysis visit following the last dose.

A final safety Follow-up Visit will be conducted 7 to 10 days after the End of Treatment or Early Termination Visit.

The study schematic is shown in Figure 1.

Figure 1. **CR845-CLIN3101 Study Schematic**



*de novo patients: not previously exposed to CR845 and not previously enrolled in CR845-CLIN2005 (Part B) and CR845-CLIN2101 (Part A)

6.2 Selection of Study Population

A screening log of potential study candidates will be maintained at each study site.

Patients providing informed consent will be screened for inclusion in the study before enrollment and dosing. All eligibility criteria must be met before a patient is enrolled. No waivers of entry criteria will be approved for this study.

Rescreening will be considered on an individual patient basis and must first be approved by the Sponsor or Medical Monitor. Patients can be assessed for rescreening if they are hospitalized during the screening process, experience an adverse event that resolves before rescreening, or are unable to enter the Treatment Period of the study due to administrative reasons (ie, missed dialysis due to extreme weather conditions).

6.2.1 Inclusion Criteria

To be eligible for inclusion into the study, a patient must meet the following criteria:

1. Willing and able to provide written informed consent prior to participating in this study;
2. Able to communicate clearly with the Investigator and staff, able to understand the study procedures, and able and willing to comply with the study schedules and all study requirements;
3. Males or females 18 years of age or older who participated in either CR845-CLIN2005 (Part B) or CR845-CLIN2101 (Part A); or de novo patients
4. Currently on hemodialysis for ESRD and has been categorized as experiencing moderate to severe uremic pruritus as part of CR845-CLIN2005 (Part B) or CR845-CLIN2101 (Part A); or de novo patients
5. Continues to experience chronic kidney disease-associated pruritus since the previous study (ie, CR845-CLIN2005 [Part B] or CR845-CLIN2101 [Part A]); de novo patients experiencing chronic kidney disease-associated pruritus at the time of Screening
6. If female:
    a. Is not of childbearing potential (surgically sterile or postmenopausal, as defined in Section 6.5.1.6); or
    b. Has a negative serum pregnancy test at screening and agrees to use acceptable contraceptive measures (as defined in Section 6.5.1.6) from the time of informed consent until the safety Follow-up Visit or 7 days after the last dose of study drug, whichever is later.
7. If male, agrees not to donate sperm after the first dose of study drug until 7 days after the last dose, and agrees to use a condom with spermicide or abstain from heterosexual intercourse during the study until 7 days after study drug administration. (Note: No restrictions are required for a vasectomized male, provided his vasectomy was performed ≥4 months prior to dosing);

8. Has a dry body weight of ≥40.0 kg at screening (prescription target dry body weight);
9. Has adequacy of dialysis, defined as meeting 1 of the following criteria during the 3 months prior to screening:
    a. ≥2 single-pool Kt/V measurements ≥1.2; or
    b. ≥2 urea reduction ratio measurements ≥65%; or
    c. 1 single-pool Kt/V measurement ≥1.2 and 1 urea reduction ratio measurement ≥65%
10. For de novo patients only, has recorded up to 4 Worst Itching Intensity NRS scores at dialysis visits over the week prior to the first dose (including the score on Day 1 of dosing), and has at least one of the NRS scores >4.

6.2.2 Exclusion Criteria

A patient will be excluded from the study if any of the following criteria are met:

1. Received an investigational drug (other than study drug received while participating in CR845-CLIN2005 [Part B] or CR845-CLIN2101 [Part A]) within 30 days prior to the first dose of study drug, or is planning to participate in another interventional clinical study while enrolled in this study;
2. Has a concomitant disease or any medical condition that, in the opinion of the Investigator, could pose undue risk to the patient, impede completion of the study procedures, or would compromise the validity of the study measurements, including, but not limited to:
    a. Known or suspected history of Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, -diagnosed alcohol, narcotic or other drug abuse, or substance dependence within 12 months prior to screening;
    b. New York Heart Association Class IV congestive heart failure (Appendix 1, Section 14.0);
    c. Severe mental illness or cognitive impairment (eg, dementia);
    d. Any other relevant acute or chronic medical or neuropsychiatric condition;
3. Abnormal liver function, defined as:
    a. Serum alanine aminotransferase or aspartate aminotransferase >2.5 times the reference upper limit of normal (ULN) at screening; and/or
    b. Total bilirubin >2 times ULN at screening.

De novo patients will be excluded if any of the additional following criteria are met at the time of entry into the study:

4. Known history of allergic reaction to opiates, such as hives or anaphylaxis (Note: side effects related to the use of opioids, such as constipation or nausea, would not exclude patients from the study).
5. In the opinion of the Investigator, has pruritus attributed to a cause other than ESRD or its complications (eg, patients with concomitant pruritic dermatological disease or cholestatic liver disease) (Note: Patients whose pruritus is attributed to ESRD complications, such as hyperparathyroidism, hyperphosphatemia, anemia, or the dialysis procedure or prescription may be enrolled);
6. Has localized itch restricted to the palms of the hands

6.3 Removal of Patients from Therapy or Assessment

6.3.1 Discontinuation of Individual Patients

A participant may withdraw from the study at any time at his/her own request for any reason without prejudice to future medical care by the physician or at the institution or may be withdrawn at any time at the discretion of the Investigator or the Sponsor for safety, behavioral, compliance, or administrative reasons.

Whenever possible, withdrawal of a patient from study drug by the Investigator should be discussed with the Medical Monitor before the patient stops study drug.

If study drug is discontinued, regardless of the reason, an Early Termination Visit is to be completed at the first dialysis after the last dose of study drug or, if not feasible during that timeframe, as soon as feasible. The Follow-up Visit is to be completed 7 to 10 days after the Early Termination Visit.

Although a patient will not be obliged to give a reason for withdrawing prematurely, the Investigator must make a reasonable effort to obtain the reason while fully respecting the patient's rights. The reason(s) for termination and date of stopping study drug must be recorded on the electronic case report form (eCRF) and source documents

If a patient discontinues early due to an adverse event, the event will be followed until resolution, the patient returns to baseline status, the condition stabilizes, or the patient is lost to follow-up.

A patient will be considered lost to follow-up when no response is received from the patient after at least 3 documented attempts to contact the patient over a minimum time of 2 weeks by the study site.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

Patients who discontinue after the administration of the first dose of study drug will not be replaced.

6.3.2 Discontinuation or Suspension of Entire Study

The Sponsor may suspend or terminate the study or part of the study at any time for any reason. If the study is suspended or terminated, the Sponsor will ensure that applicable regulatory agencies and Institutional Review Boards (IRBs)/Independent Ethics Committees are notified, as appropriate.

Should the study be closed prematurely, all study materials (eg, completed, partially completed, and blank eCRFs, as well as study drug) must be returned to Cara Therapeutics or destroyed at the site according to instructions which will be provided by the Sponsor, as applicable.

6.4 Treatment

Additional information on the study drug and its preparation, administration, storage, supply, disposition, and accountability can be found in the Pharmacy Section of the Investigator Site File (ISF).

6.4.1 Identity of Investigational Product(s)

6.4.1.1 Formulation of Study Drug

Study drug will be supplied by the Sponsor as a solution in 2-mL glass vials containing a minimum extractable volume of 1.3 mL of CR845 at a concentration of 0.05 mg/mL in 0.04 M isotonic acetate buffer, pH 4.5. The composition of the CR845 solution contains CR845 (free base), acetic acid, sodium acetate trihydrate, sodium chloride, hydrochloric acid, and water for injection.

6.4.1.2 Packaging, Labeling, and Storage Stability of Study Drug

Study drug will be shipped at 15°C to 30°C. Temperature will be monitored during shipment and verified and recorded in the pharmacy log by pharmacist upon arrival at the site. The vials must be stored at temperature ranging from 15°C to 30°C upon receipt and temperature should be monitored accordingly.

Vials will be packaged in boxes containing 24 vials per box.

Labeling of the vials will include the following:

- Study protocol number (CR845-CLIN3101)
- Name and concentration of study drug (CR845 0.05 mg/mL)
- Batch or lot number
- Retest date
- Temperature storage instructions (store at 15°C to 30°C)

- Extractable volume: at least 1.3 mL
- Name and location of Sponsor
- Administration according to protocol
- Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use

The label on each box will be the same as the label on an individual vial, and in addition, will provide the number of vials contained per box (24) and the statement "*For Clinical Trial Use Only*".

6.4.1.3 Individual Dose Labeling

The study drug will be dispensed by qualified staff members who have received training on study drug handling and administration.

One syringe will be prepared for each patient on each dosing day. Patients weighing >135.0 kg require modified preparation of CR845. Syringes and syringe labels will be provided. Refer to the Pharmacy Section of the ISF for details.

6.4.2 Drug Accountability

All supplies will be maintained under adequate security by the pharmacist or approved staff at the investigational site. At the end of each injection, the used vials will be stored until the study monitor performs accountability. Details of study drug accountability and return are provided in the ISF.

The Sponsor (or delegated person) will be permitted, at intervals and upon request during the study, to check the supplies, storage and dispensing procedures, and records.

Retention samples of the study drug will be retained by the manufacturer(s) on behalf of the Sponsor for 2 years after completion of the study.

6.4.3 Method of Assigning Patients to Treatment Groups

All eligible patients will receive CR845 at a dose of 0.5 mcg/kg starting on Day 1 of the Treatment Period.

6.4.4 Preparation of CR845

Volume of CR845 to be administered will be based on patient's prescription target dry body weight recorded on Day 1, and adjusted monthly if target dry body weight changes ±10% or more from Day 1 target dry body weight.

A single vial of CR845 will be used for patients with a target dry body weight ≤135 kg. For patients with a target dry body weight >135 kg, 2 vials of CR845 will be used to

ensure that the full volume of study drug can be prepared. Further details will be provided in the ISF.

6.4.5 Administration of CR845

Patients will receive IV CR845 at a dose of 0.5 mcg/kg after each dialysis session, generally 3 times per week for up to 52 weeks as an IV bolus into the venous line of the dialysis circuit at the end of each dialysis session and may be given either during or after rinse back of the dialysis circuit. If a patient receives additional dialysis during a given week for any reason, an additional dose of CR845 will be administered following dialysis. A maximum of 4 doses per week is allowed. No additional doses will be given for patients receiving an additional unscheduled ultrafiltration treatment.

Following the IV push of study drug, the venous line must be flushed with at least 10 mL of normal saline.

6.4.6 Management of Missed Doses

If a patient misses a dialysis visit and the planned dose of CR845 for that visit, dosing should resume at the next dialysis visit.

Contact the Medical Monitor if a patient misses ≥3 consecutive doses of CR845 at any time during the Treatment Period or ≥4 doses within a period of 4 weeks.

6.4.7 Blinding

No blinding is required for this open-label study.

6.4.8 Prior, Concomitant, and Prohibited Medications

6.4.8.1 Prior and Concomitant Medications

Prior medications (including vitamins and herbal supplements) are defined as those that the patient has taken any time during the last month prior to the first dose of study drug on Day 1. Concomitant medications are medications that are taken from after the start of the first dose of study drug on Day 1 through the end of the Treatment Period (ie, End of Treatment/Early Termination Visit). Only medications that are used for adverse events will be recorded from the time after the End of Treatment/Early Termination visit through the Follow-up Visit.

The dose and type of ESAs and IV iron administered will be recorded as a total over a 4-week period as per SOE (Table 1). Use of antipruritic medications will be recorded on an ongoing basis.

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 scheduled visit and noted on the appropriate page of the eCRF, as applicable.

6.4.8.2 Restricted and Prohibited Medications

There will be no restricted medications for this study. However, all new concomitant medications or change of frequency and doses of a concomitant medication will need to be recorded.

6.5 Study Assessments and Procedures

Study procedures described in this protocol are summarized in Table 1. No efficacy assessments are planned for this study.

An ICF will need to be signed prior to initiation of the Screening Visit and any procedures that follow.

The safety assessment visit may occur on any chosen dialysis day of a scheduled week as long as all assessments are completed during that visit. Patients who miss one of the scheduled study visit weeks (eg, Week 4) may complete this visit at their next dialysis treatment if conducted within 2 weeks of the scheduled visit.

Unscheduled visits may be necessary for outstanding, unresolved adverse events (eg, additional safety laboratory or clinical evaluations). At minimum, for any unscheduled visit, the reason for the visit will be recorded, the adverse events reported, as well as changes to concomitant medications as applicable. Additional testing (eg, laboratory tests, vital signs, ECGs) will be performed as clinically indicated.

Table 1. Schedule of Events

Study Procedures	Screening[b]	Treatment Period[a] Up to 52 Weeks						Follow-Up
		Day 1	Week 4	Week 12	Week 24	Week 36	End of Treatment / Early Termination	7 - 10 days after End of Treatment / Early Termination
Administrative procedures								
Informed consent	X							
Inclusion/exclusion criteria	X	X[c]						
Safety and other evaluations								
Physical examination	X						X	
Record target dry body weight[d]	X	X	[Record every 4 weeks][d]					
Post-dialysis weight (measured weight)		X	X	X	X	X	X	
Pre-dialysis 12-lead electrocardiogram[e]	X			X	X		X	
Pre-dialysis vital signs[f]	X	X	X	X	X	X	X	X
Hematology, serum chemistry (pre-dialysis)	X	X	X	X	X	X	X	
Serum pregnancy test for women of childbearing potential only	X			X	X	X	X	
Worst Itching Intensity NRS (De novo patients only)[k]	X	X						
Record ESA and IV iron usage			X[g]	X[g]	X[g]	X[g]	X[g]	
Record number of missed dialysis visits and reason(s) + incidence of infection and use of antibiotics, as applicable			[Record on an ongoing basis][h] →					

Table 1. Schedule of Events (Continued)

Study Procedures	Screening[b]	Treatment Period[a] Up to 52 Weeks						Follow-Up
		Day 1	Week 4	Week 12	Week 24	Week 36	End of Treatment / Early Termination	7 - 10 days after End of Treatment / Early Termination
Safety and other evaluations								
IV administration of study drug after dialysis, including record of start and stop time of dialysis		X[i]	[Dose after each dialysis up to Week 52 included][i]					
Inflammatory biomarker samples[j]		X		X	X	X	X	
Adverse event monitoring	X	[Record on an ongoing basis][h] →						
Concomitant medications (including antipruritic medications)	X	[Record on an ongoing basis][h] →						
In-patient hospitalization and/or EDE/OBS	X	[Record on an ongoing basis][h] →						

EDE = emergency department encounter; ESA = erythropoiesis-stimulating agent; IV = intravenous; OBS = observation stay

[a] Each visit during the Treatment Period will coincide with the patient's normal dialysis treatments. The safety assessment visit may occur on any chosen dialysis day of a scheduled week as long as all assessments are completed during that visit. Patients who miss one of the scheduled study visit weeks (eg, Week 4) may complete this visit at their next dialysis treatment if conducted within 2 weeks of the scheduled visit date. The End of Treatment visit will be the first dialysis visit following the last dose of study drug (i.e. first dialysis on Week 53).

[b] Screening assessments to be conducted up to 14 days prior to start of the Treatment Period on Day 1. Rescreening will be considered on an individual patient basis and must first be approved by the Sponsor or Medical Monitor (see Section 6.2).

[c] Prior to dosing on Day 1 of the Treatment Period, the inclusion/exclusion criteria will be confirmed.

[d] The prescription target dry body weight will be captured from the dialysis prescription and will recorded on Day 1 and at the end of every 4 weeks during the Treatment Period (Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52). The date of prescription will also be recorded.

[e] Electrocardiogram must be performed prior to start of dialysis.

[f] Vital signs, including body temperature, heart rate, and blood pressure, will be obtained while the patient is in a sitting or semi-recumbent position prior to start of dialysis.

[g] Total doses of ESA and IV iron administered will be recorded for the 4-week period ending on Weeks 4, 12, 24, 36, and 52.

[h] Adverse events, concomitant medications, and in-patient hospitalizations and/or EDE/OBS will be recorded during the study starting at the Screening Visit.

[i] Administered after each dialysis as an IV bolus. Details in Section 6.4.5.

[j] Biomarker samples must be collected prior to the start of dialysis.

[k] NRS worksheet will be completed at up to 4 dialysis visits for de novo patients (only) during the week prior to the first dose (Day -7 to Day 1) with training conducted on the first dialysis visit on Day -7. One of 4 scores must be >4 for the patient to be included in the study. These criteria for eligibility should not be communicated to the patients.

6.5.1 Safety Assessments

The safety assessments for each patient are the following:

- Severity, seriousness and relationship of adverse events to study drug
- Physical examination
- Vital signs
- 12-lead ECGs
- Clinical laboratory tests

6.5.1.1 Adverse Events

6.5.1.1.1 Definition of Adverse Event

An adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

In this study, adverse events will be captured from the time a patient signs the ICF to the last follow-up visit and include the following:

- Any new sign, symptom, or disease;
- Any new clinically significant or symptomatic laboratory/diagnostic test abnormality;
- Any clinically significant worsening of laboratory/diagnostic test abnormality;
- Any worsening (ie, clinically significant change in frequency, nature and/or intensity) of a pre-existing condition.

A pre-existing condition is a condition that is present prior to signing the ICF for the study. Pre-existing conditions, such as illnesses, symptoms, reactions, progression of disease states, and other comorbidities, as well as laboratory/diagnostic test abnormalities, should be documented in the patient's record as medical history.

Signs and symptoms should be reported individually as adverse events (nonserious), unless a medical diagnosis was provided.

Any adverse event that satisfies any of the seriousness criteria described in Section 6.5.1.1.3 should be reported as an SAE using the SAE Report Form, in addition to documenting in the eCRF. Medical diagnosis, whenever provided, should be reported rather than individual signs and symptoms.

Any incident of pregnancy in a study participant or in the partner of a study participant occurring after the study participant has signed the ICF should be reported using the Pregnancy Reporting Form, in addition to documenting in the eCRF.

6.5.1.1.2 Adverse Event Severity Assessment

The Investigator will assess the severity (ie, intensity) of each adverse event (serious and nonserious) reported during the study based on his/her clinical judgment. The severity of each adverse event should be assigned to one of the following categories:

Mild:	Transient, requires no special treatment, is easily tolerated by the patient, causes minimal discomfort, and does not interfere with the patient's daily activities
Moderate:	Introduces a level of inconvenience or concern to the patient that may interfere with daily activities, but usually is ameliorated by simple therapeutic measures
Severe:	Interrupts a patient's usual daily activity and requires systemic drug therapy or other treatment

6.5.1.1.3 Definition of Serious Adverse Events

An SAE is any untoward medical occurrence that:

- Results in death;
- Is life-threatening;

  NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity; or
- Is a congenital anomaly/birth defect.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse.

6.5.1.1.4 Severe versus Serious Adverse Event

The term "severe" is 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). An adverse event as well as an SAE must be assessed for severity. An adverse event that is assessed as severe should not be confused with an SAE. "Severity" is not the same as "Serious," which is based on 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.

6.5.1.1.5 Adverse Event Causality or Relatedness to the Study Drug

Every effort should be made by the Investigator to explain each adverse event and assess its relationship, if any, to study drug. The Investigator should consider many factors, including, but not limited to, temporal association of the event and date/time of study drug, duration of study drug, medical/biologic plausibility, pharmacology and adverse event profile of study drug, medical history (past medical history, underlying disease, co-morbidities, intercurrent illness), concomitant medications, medical judgment, dechallenge, rechallenge, drug interaction, other plausible causes, etc., to determine the causality assessment of an event.

The Investigator as well as the Sponsor will determine adverse event/SAE causality as 'Related' or 'Not Related' to study drug. Although there is no international consensus on how to define 'Related' and 'Not Related,' in general, an event is considered 'Related' if there is reasonable possibility that the event is related to study drug than to any other possible cause(s). Conversely, an event is considered 'Not Related' if there is reasonable possibility that the event is related to other factors than the study drug.

6.5.1.1.6 Adverse Event Documentation and Follow-Up

All adverse events, including observed, elicited, or volunteered problems, complaints, or symptoms are to be recorded on the adverse event page in the patient's eCRF from the time the patient signs the ICF and until the Follow-up Visit/early termination whether or not judged by the Investigator to be related to study drug. The need to capture this information is not dependent upon whether adverse events are related to study drug. Serious adverse events that occurred up to 30 days after the last dose of study drug need to be documented on an SAE Report Form if they are deemed by the Investigator to be "Related" to study drug.

Each adverse event is to be documented with a verbatim/reported term, start and stop date and time, severity, causal relationship to study drug, action taken with study drug, and outcome (resolved, resolved with sequelae, resolving, fatal, unknown). The Investigator must review new adverse events and the outcome of ongoing adverse events frequently throughout the study.

In addition to recording all adverse events (serious and nonserious) in the patient's eCRF, all SAEs must also be documented on the SAE Report Form for the study.

The Investigator should follow all adverse events until they resolve, the Investigator assesses them to be stable, or the patient's participation in the study ends, whichever comes first. In addition, the Investigator should follow all adverse events assessed as related to study drug that are ongoing at the time of the patient's last visit, until they resolve or the Investigator assesses them as stable, even if the patient's participation in the study has ended. Resolution of such events is to be documented in the patient's record as appropriate.

It is anticipated that some patients may undergo procedures and/or experience events that are common in the study population under investigation, independent of study therapy. Preplanned procedures and procedures (eg, kidney transplant, catheter replacement) or events that are independent of study therapy, according to the Investigator's assessment, should be documented as specified in the Safety Management Plan. Common procedures or events (new or ongoing) for which the Investigator cannot rule out the role of study drug in their evolution, either because their nature or severity is not consistent with that generally seen in the study population or because of other valid medical/scientific rationale, should be recorded and reported as adverse events with all the attributes required for appropriate medical assessment.

6.5.1.1.7 Serious Adverse Event Notification, Documentation, and Reporting

The Investigator will report an SAE within 24 hours of becoming aware of the event. An SAE Report Form will be completed regardless of relationship to the study drug. The initial report will not be delayed in order to obtain additional information. Any additional information will be reported as a follow-up to the initial report within 24 hours of collection.

Details for reporting and follow-up of SAEs are provided in the ISF.

In the event of any SAE (other than death) occurring after the last dose of study drug and prior to the Follow-up Visit, the patient will be instructed to contact the Investigator or designee immediately using the instructions provided on the ICF.

The Medical Monitor will review reported SAEs and may contact the Investigator directly for further information.

The Sponsor will comply with the applicable local regulatory requirements related to reporting of SAEs to the Food and Drug Administration (FDA), while the Investigator and designated study personnel will comply with the applicable local regulatory requirements related to reporting of SAEs to the IRB and Sponsor.

It is the responsibility of Cara Therapeutics to send all regulatory reports to the FDA. Adverse events that are serious, related to the study drug, and unexpected (per the

Investigator's Brochure [IB]) will be reported to the FDA as per Code of Federal Regulations (CFR) 21 CFR 312.32 on Investigational New Drug (IND) safety reporting and as specified in the Safety Management Plan.

For regulatory reporting purpose, the Sponsor will follow "Guidance for Industry and Investigators - Safety Reporting Requirements for INDs and BA/BE Studies" (December 2012), which states "for serious events that are unexpected, the Sponsor considers the investigator's causality assessment but submits an IND safety report only for those events for which the Sponsor determines there is a reasonable possibility that the drug caused the event, regardless of the investigator's causality assessment."

As applicable, the Sponsor will also notify other participating Investigator(s) of all IND Safety Reports to ensure prompt notification of significant new adverse events or risks with respect to study drug. This notification will occur as soon as possible and in compliance with country-specific regulations.

Refer to the ISF for further details about SAE reporting and processing. The Medical Monitor should be contacted by study sites requiring additional clarification on an SAE.

6.5.1.2 Physical Examination

Physical examinations will include, at a minimum, an examination of the heart, lungs, abdomen, extremities, and neurological and vascular systems. Clinically significant abnormalities prior to signing the ICF will be reported as medical history and clinically significant new or worsening findings observed after the signature of the ICF will be reported as adverse events.

6.5.1.3 Vital Signs

Vital signs include sitting or semi-recumbent (for at least 3 minutes) body temperature, heart rate, and blood pressure and will be measured prior to start of dialysis.

Measurements will be repeated if a value is out of the reference range due to a technical issue, considered abnormal for the patient, or for other medical concerns. Only the repeated measurement will be recorded.

In the event of a clinically significant change in blood pressure and/or heart rate, the Investigator and dialysis staff should evaluate and manage the patient per standard dialysis unit practices with knowledge of the patient's typical blood pressure and heart rate excursions.

6.5.1.4 Electrocardiogram

The 12-lead ECGs will be obtained prior to the start of dialysis and will be read locally by the Investigator or qualified designee. An ECG read by a qualified designee must be endorsed by the Investigator. Clinically significant abnormalities or worsening findings observed after the first dose of study drug will be reported as TEAEs.

6.5.1.5 Clinical Laboratory Tests

Blood samples for clinical laboratory tests will be taken prior to dialysis and the following will be analyzed by one of the central laboratories. Processing and shipment of central laboratory samples will be described in the Laboratory Manual.

Hematology:	Hemoglobin, hematocrit, platelet count, white blood cell count (including differential)
Serum chemistry:	Total bilirubin, direct bilirubin (if total bilirubin is above the ULN), alkaline phosphatase, alanine transaminase, aspartate aminotransferase, glucose (nonfasting), blood urea nitrogen, creatinine, albumin, and electrolytes (sodium, potassium, chloride, calcium and phosphorus)
Serum pregnancy:	Women of childbearing potential only

6.5.1.6 Contraception and Pregnancy

All females are considered to be of childbearing potential unless they are:

- Surgically sterile (ie, tubal ligation, bilateral oophorectomy, and/or hysterectomy) or
- Postmenopausal

Once they have consented to participate in the study, all women of childbearing potential will be counseled on the importance of avoiding pregnancy and on the need to practice adequate birth control for the duration of the study, from screening until 7 days after the last dose of study drug.

Medically acceptable methods of birth control are methods with a failure rate of <1% per year, which include hormonal contraceptives for at least 1 cycle of treatment before study enrollment, an intrauterine device, and double-barrier method (eg, male or female condom, diaphragm).

Per inclusion criteria, male patients will agree not to donate sperm after the first dose of study drug until 7 days after the last dose, and will agree to use a condom with spermicide or abstain from heterosexual intercourse during the study until 7 days after study drug administration. No restrictions are required for a vasectomized male, provided his vasectomy was performed ≥4 months prior to dosing.

Women will be counseled to contact the Investigator or his/her staff immediately if pregnancy is suspected. Males will be instructed to report to the Investigator if their partner becomes pregnant during the study.

If a patient becomes pregnant during the Treatment Period or within 7 days after the last dose of study drug, the Investigator will immediately discontinue the patient from the study and contact the Sponsor or designee. Diligent efforts will be made to determine the outcome for all pregnancies in the clinical study. Information on the status of the mother and the child will be forwarded to the Sponsor. Generally, follow-up will occur within 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported. Both maternal and paternal exposure will be collected. For exposure involving the female partner of a male patient, the necessary information must be collected from the patient while respecting the confidentiality of the partner. A pregnancy report will be completed.

6.5.2 Other Assessments

6.5.2.1 Infections

Infections will be recorded as per standard procedures at the dialysis sites and reported on the adverse event eCRF page.

6.5.2.2 Use of Iron, ESA, Antibiotics and Antipruritic Agents

Use of antibiotics, ESA, iron and antipruritic medications will be recorded and reported on the appropriate eCRF page.

6.5.2.3 Hospitalization and/or EDE and OBS

In-patient hospitalizations will be collected on the SAE form. EDE and OBS details will be captured on a separate eCRF page.

6.5.2.4 Anti-inflammatory Biomarkers

Inflammatory biomarkers such as, but not limited to, hepcidin, interleukin (IL)-1, IL-2Rα, IL-6, IL-8, IL-31, tumor necrosis factor, interferon, monocyte chemoattractant protein, and C-reactive protein will be measured, as defined in the statistical analysis plan (SAP). A blood sample of sufficient volume to provide for replicate assays of each biomarker will be collected prior to dialysis per the schedule of events (

Table 1) during the Treatment Period. The actual time of sample collection will be recorded.

Detailed instructions for biomarker sample collection and processing will be provided in the laboratory manual.

6.5.2.5 Worst Itching Intensity Numerical Rating Scale

It will be necessary to confirm that de novo patients have moderate-to-severe pruritus as measured by the 24-hour Worst Itching Intensity numerical rating scale (NRS) (Appendix 2, Section 14.2). NRS scores will be collected at each dialysis visit in the week prior to first dose (including the score on Day 1 of dosing) for a total of 4 scores. To be eligible for participation, at least 1 NRS score must be >4. These criteria for eligibility should not be communicated to the patients.

Patients will be asked to indicate the intensity of the worst itching they experienced over the past 24 hours by marking one of 11 numbers, from 0 to 10, that best describes it, where "0" is labeled with the anchor phrase "no itching" and "10" is labeled "worst itching imaginable." Patients will be provided with these worksheets to record their 24-hour worst itching assessment scores at the clinic on dialysis days on Day -7 to Day 1, inclusive.

7.0 Discussion and Justification of Study Design

7.1 Discussion of Study Design and Choice of Control Groups

This is an open-label study designed to evaluate the safety of CR845 0.5 mcg/kg IV administered after each dialysis session (generally 3 times per week for up to 52 weeks) in hemodialysis patients who previously participated in CR845-CLIN2005 (Part B) or CR845-CLIN2101 (Part A), and in de novo patients who did not previously participate in CR845-CLIN2005 (Part B) or CR845-CLIN2101 (Part A). Amendment 1.0 is to allow the enrollment of de novo patients. There are no additional safety concerns regarding enrolling de novo patients.

This design is commonly used in clinical development to obtain long-term safety information. The duration of the study is in accordance with International Council for Harmonisation (ICH) and FDA guidance [Guidance for Industry February 2016].

7.2 Selection of Doses in the Study

The combined safety, PK, and efficacy data from CR845-CLIN2101 (Part A) provided the basis for the selection of the dose and dose regimen of CR845 to be used in this study. The lowest dose tested (0.5 mcg/kg IV) appeared to be safe, well-tolerated, and effective at reducing itch intensity over a period of 8 weeks.

7.3 Appropriateness of Measurements

Standard clinical, laboratory and statistical procedures and methodology will be utilized in this study.

8.0 Statistical Methods

8.1 General Considerations

A SAP will be developed based on the clinical protocol and eCRFs. No database may be locked or analyses completed until the SAP has been approved.

The SAP will provide a detailed description for the handling of missing data, patient eligibility criteria for the analysis, and statistical methodology. This protocol describes key analyses as currently planned. If differences occur between analyses described in the SAP and the current protocol, those found in the SAP will assume primacy.

Unless otherwise noted, continuous variables will be summarized using number of nonmissing 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.

All analyses will be performed using SAS® version 9.2 or higher, unless otherwise specified.

8.2 Determination of Sample Size

Approximately 300 male and female hemodialysis patients who previously participated in either CR845-CLIN2005 (Part B) or CR845-CLIN2101 (Part A) and hemodialysis patients who had not been previously exposed to CR845 and did not previously participate in the Phase 2 studies CR845-CLIN2005 (Part B) or CR845-CLIN2101 (Part A) (de novo patients) will be enrolled in this study. No sample size calculation was performed to select this sample size.

8.3 Randomization

No randomization will be performed for this study. All patients who enrolled in this study will receive CR845 at a dose of 0.5 mcg/kg.

8.4 Interim Analysis

No interim analysis is planned. However, an ongoing review of the cumulative safety data for this study will be conducted by the Sponsor or designee.

8.5 Analysis Populations

The Safety Population is defined as all enrolled patients who received at least 1 dose of study drug. The Safety Population will be used to analyze all safety data.

8.6 Statistical Summary and Analysis

8.6.1 Patient Disposition

The number of patients enrolled, completed, or discontinued from the study, along with the reason for discontinuation, will be presented.

Patient count by analysis population will also be tabulated.

For all categories of patients (except for the screened patients), percentages will be calculated using the number of enrolled patients as the denominator.

8.6.2 Protocol Deviations

Protocol deviations will be identified in several ways: through programmatic checks, through medical reviews, and by clinical research associates during site monitoring. Protocol deviations will be classified as minor or major prior to the database lock. Major protocol deviations will be summarized. All protocol deviations will be listed.

8.6.3 Demographic and Baseline Characteristics

Demographic and baseline variables will be summarized to include the following:

- Age (years) at screening
- Age category at screening (<45, 45-<65, 65-<75, ≥75)
- Gender
- Ethnicity
- Race
- Height (cm)
- Target dry body weight (kg)

Age will be calculated using the following formula:

Age = (date of the screening visit – the date of birth + 1)/365.25.

Baseline characteristics of the disease will also be summarized for the following:

- Years since ESRD
- Years on chronic hemodialysis
- Baseline single pool Kt/V (spKt/V)
- Baseline urea reduction ratio
- Etiology of chronic kidney disease

Similarly, years since ESRD will be calculated as:

(Date of the screening visit – first date of ESRD + 1)/365.25.

Years on chronic hemodialysis will be calculated as:

(Date of the screening visit – date of first chronic hemodialysis + 1)/365.25.

All demographic and other baseline characteristics will also be provided in a listing.

8.6.4 Medical History

Medical history data will be coded using Medical Dictionary for Regulatory Activities (MedDRA). A summary table will be presented by the MedDRA SOC and PT. The data will also be listed, including medical history presented by SOC, PT, medical condition, start date, end date, and whether or not the condition is ongoing.

8.6.5 Prior and Concomitant Medications

All medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). All prior and concomitant medications (see Section 6.4.8.1) will be listed and summarized in a table. Additionally, a listing of unique medications and their corresponding coding will be presented.

Medications will be reported by drug class (Anatomical Therapeutic Chemical [ATC] 3) and preferred term; a patient will be counted only once for each of these.

8.6.6 Antipruritic Medication

An additional analysis of antipruritic medications identified as medications where 'Yes' is checked on the *Previous or Concomitant Medications CRF page* to the question 'Was this medication used to treat pruritus?' will be conducted. These medications will be summarized by ingredient rather than by drug class (ATC3).

8.6.7 Measurements of Treatment Compliance

For this study, the duration of treatment for each individual patient is expected to be 52 weeks, for a total of approximately 156 doses of study drug administered immediately following each dialysis session. The overall study duration for each individual patient is expected to be up to 57 weeks.

The following variables will be summarized:

- Duration of treatment (days)
- Duration of study (days)
- Total number of doses actually received (eg, 1-12, 13-36, 37-72)

- Number of missed doses
- Total treatment exposure in patient-years

Duration of treatment (days) = (date of first dialysis after last dose) – (date of first dose) + 1.

Duration of study (days) = (end of participation date) – (date of first dose) + 1.

Patient-years = total duration of treatment (days) of all patients divided by 365.25.

If a patient receives additional dialysis during a given week for any reason, an additional dose of CR845 will be administered following dialysis. A maximum of 4 doses per week is allowed. No additional doses will be given for patients receiving an additional unscheduled ultrafiltration treatment. The number of patients getting such an extra treatment will be summarized.

Missed and extra doses will be determined as follows:

1. Individual weeks for each patient are examined.
2. Each patient should have 3 doses per week up to Week 52. Anything more will count as extra doses; anything less will be counted as missed doses.
3. Patients who do not complete through Week 52 will be checked for how far they were into the week that they discontinued: 1,2 days means that they should have 1 dose; 3,4 = 2 doses; 5 or more =3 doses. This will be compared to actual doses for that week to determine missed/extra.
4. The missed and extra doses will then be summed across each patient's weeks to get the total missed and extra.

8.7 Safety Analysis

Analysis of all safety data will be performed on the Safety Population. The SAP will provide further detail for the analyses to be applied to each safety parameter.

The objective of the evaluation of the safety variables is to evaluate the data related to adverse events, vital signs, ECGs, and clinical laboratory tests. No statistical hypothesis testing will be carried out and no inferential statistical analysis of the safety parameters will be performed.

Summaries of outcome measures by visit will be presented in tables and listings.

The baseline value for all safety parameters will be defined as the last value obtained prior to the first dose of study drug and will include both scheduled and repeat (unscheduled) observations.

All tables will be presented overall, by the de novo classification of the patients and by treatment group as CR845 and Placebo for the patients who participated in the lead-in

studies; all listings will include columns to identify the patient's de novo classification and treatment assignment in the lead-in studies as applicable.

8.7.1 Adverse Events

All adverse events will be coded using the MedDRA to map adverse event verbatim to the corresponding MedDRA SOC and PT for standardization and summary purposes.

All reported adverse events (whether or not treatment-emergent) will be included in a by-patient adverse event listing. Only TEAEs will be included in summary tables. Treatment-emergent adverse events are identified as any adverse event starting after the first dose of the study drug up to the study Follow-up Visit or Early Termination Visit (or 7 to 10 days after the last dose if no Early Termination Visit was conducted). The number and percentage of patients experiencing TEAEs will be summarized. A patient will be counted only once in the incidence count for a MedDRA SOC or PT, although a patient may have multiple occurrences (start and stop) of an event associated with a specific MedDRA PT or SOC. The most frequent TEAEs will also be tabulated by SOC and PT.

The incidence and percentage of patients experiencing treatment-emergent SAEs and TEAEs leading to study discontinuation will be presented by the appropriate MedDRA SOC and PT.

Treatment-emergent adverse events will also be summarized by severity and relationship. If the severity and/or relationship to the study drug of an adverse event is missing, a worst-case scenario will be assumed (ie, the adverse event will be categorized as "severe" and/or "related" to the study drug). Treatment-emergent deaths will also be summarized by cause and relationship to study drug.

8.7.2 Clinical Laboratory Evaluations

Summary statistics for each scheduled time point measured and mean changes from baseline to each time point (when applicable) will be presented for clinical laboratory results.

Laboratory values will be reported in both standard and Système International units.

Laboratory test results will be assigned an L/N/H classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Comparisons will be based on 3×3 tables (shift tables) that, for a particular laboratory test, compare the baseline L/N/H classification to the highest and/or lowest L/N/H classification during the treatment period. Clinically important lab values based on prespecified criteria defined in the SAP will also be summarized.

8.7.3 Vital Signs and ECGs

Summary tables will include descriptive statistics (number of patients, mean, standard deviation, median, minimum, and maximum) for baseline and each postbaseline assessment. Descriptive statistics will be calculated on both the actual score and the change from baseline score. If 2 or more evaluations occur in the same visit window, the evaluation closest to the target visit day will be selected for inclusion in the analysis. If multiple evaluations are equally close to the target visit day, then the latest evaluation will be selected for inclusion in the analysis.

All vital sign summaries will include the patients in the Safety Population who have at least a postbaseline assessment (for criteria based on postbaseline assessments) and with both a baseline and at least 1 postbaseline assessment (for criteria evaluating changes from baseline).

A second summary will focus on the individual patient measures with the intent of identifying postbaseline abnormalities defined as clinically significant. Clinically significant vital signs will defined based on prespecified criteria presented in the SAP.

Descriptive statistics will summarize the postbaseline patient frequencies (percentages) that are outside the range defined for each vital sign measure.

The number and percentage of patients meeting the criteria for each of the prespecified categories will also be presented. All vital signs will be listed in by patient listings including visit and collection date/time, and will be sorted by patient identifier and date/time of assessment.

Electrocardiogram results include an overall interpretation of 'normal,' 'abnormal but not clinically significant,' or 'abnormal and clinically significant.' These results will be tabulated at each time point.

Clinically significant abnormalities at screening will be recorded as medical history. Clinically significant abnormalities or worsening of ECG findings observed after the first dose of study drug should be reported as adverse events.

Electrocardiogram results will be listed for each visit, including visit, whether ECG was performed (yes/no), explanation (if not performed), assessment date/time, study date, overall interpretation, and relevant medical history number or adverse event number, if deemed a clinically significant abnormality.

8.8 Other Assessments

8.8.1 In-patient Hospitalization, EDE, and OBS

Incidence of in-patient hospitalization will be summarized based on information collected on the hospitalization page. The proportion of patients who had inpatient hospitalization and the summary statistics for the hospitalization (eg, reason for hospitalization, duration,

dialysis, and IP treatment during hospitalization [yes/no]) will be summarized. Similar analyses will be performed for EDE and/or OBS visits.

8.8.2 Missed Dialysis Visits and Incidence of Infection

Missed dialysis visits will be summarized based on the percentage of patients who missed 1 or more dialysis visits and total number of missed dialysis visits during the Treatment Period.

The incidence of infections will be summarized based on adverse events, hospitalizations, and/or use of antibiotics for treatment of infection.

8.8.3 ESA and IV Iron Usage

The dose and type of ESAs and IV iron administered at each dialysis visit and at the end of treatment will be recorded on the ESA log of the eCRF and Parenteral (IV or dialysate) Iron Log of the eCRF, respectively.

The baseline ESA will be defined as the average ESA dose for each patient during the 4 weeks prior to Day 1. The average ESA dose across dialysis visits during each month will also be calculated. Change from baseline will be calculated. A similar definition applies to change from baseline in IV iron dose (mg).

8.8.4 Inflammatory Biomarkers

Changes in inflammatory biomarkers from pre-dose to the end of the Treatment Period will be summarized descriptively.

9.0 Quality Control and Quality Assurance

9.1 Study Monitoring Plan

Monitoring and auditing procedures that comply with current Good Clinical Practice (GCP) guidelines will be followed, including remote and onsite review of the eCRFs via an electronic data capture system for completeness and clarity, source document verification, evaluation of protocol adherence, appropriate documentation of informed consent procedures, safety reporting, study drug storage, and dispensation. The study will be monitored by Cara Therapeutics or its designee (contract research organization). Monitoring will be done remotely or by personal visits from a representative of the Sponsor or its designee (site monitor) who will review patient enrollment, eCRFs, source documents, drug accountability records, and reporting and recording of adverse events. 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).

The site monitor(s) will follow written standard operating procedures as agreed with the contract research organization and the Sponsor. The site monitor(s) will verify that the clinical study 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 as per details described in a clinical monitoring plan for this study.

9.2 Audits and Inspections

The investigational site will maintain appropriate medical and research records for this study, in compliance with ICH-GCP, 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 study necessary for the reconstruction and evaluation of the study. 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 study, as applicable.

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

9.3 Data Collection, Validation, and Analysis

A data management vendor 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.

10.0 Ethics and Regulatory Compliance

10.1 Independent Ethics Committee or Institutional Review Board

A properly constituted, valid IRB or Independent Ethics Committee must review and approve the protocol, the Investigator's ICF, and related patient information and recruitment materials (if applicable) before the start of the study. It is the responsibility of the Investigator to ensure that written informed consent is obtained from the patient before any activity or procedure is undertaken that is not part of routine care.

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, IB, ICF, 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. Except for changes necessary to eliminate an immediate hazard to study patients, or when the change involves only logistical or administrative aspects of the study (eg, change in monitor, change of telephone number), no amendments to the study protocol should be made without the prior written agreement of the Sponsor and acknowledgement by the Investigator and, as applicable, the IRB.

The Investigator(s) will maintain documentation of the composition of the IRB as well as all correspondence with the IRB. The Investigator(s) 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 provide Cara Therapeutics or its designee copies of all IRB approval notices, correspondence, annual reports, and final study progress reports.

10.2 Ethical Conduct of the Study

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki and all accepted 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.

The Investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol, IB, and any other study-related manual(s). Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. A study master file must be established for the study, and retained according to the appropriate regulations.

10.3 Informed Consent Process

Informed consent is required for all patients participating in this study. In obtaining and documenting informed consent, the Investigator must comply with applicable regulatory requirements and must adhere to GCP regulations. It is the responsibility of the Investigator to ensure that written informed consent is obtained from the patient before any activity or procedure is undertaken that is not part of routine care.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and that continues throughout the individual's study participation. The Investigator or designee will discuss extensively with the participant patient the study risks. Copies of the current, IRB-approved ICF detailing the risks and benefits of study participation will be provided to the participants. 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 participation in the study. 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 study. A signed copy of the ICF will be given to the participants for their records.

10.4 Patient Confidentiality

In order to maintain patient privacy, all eCRFs, study drug accountability records, study reports, and communications will identify the patient by assigned patient number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee, and regulatory authority(ies) 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 study 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.

11.0 Data Handling and Quality Assurance

All participant data relating to the study will be recorded on eCRFs unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The Investigator must permit study-related monitoring, audits, IRB/Independent Ethics Committee review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH-GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 2 years after the marketing approval of the study drug or after discontinuing clinical development unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor. 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 Therapeutics must be notified in writing.

12.0 Administrative Procedures

12.1 Protocol Adherence

It is vital to the success of the study that the Investigator adhere to the details of the protocol, and thus to keep 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 and will be documented. Protocol deviations due to lack of patient compliance must also be documented.

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

12.2 Publication of Study Findings

All information regarding CR845 provided by Cara Therapeutics to the Investigator is privileged and confidential information. 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 Therapeutics. The Investigator agrees to use the information to accomplish the study and will not use it for other purposes without written permission from Cara Therapeutics. Partial or full data or results from this study cannot be published without express written consent from Cara Therapeutics. It is understood that there is an obligation to provide Cara Therapeutics 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.

13.0 References

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14.0 Appendix

14.1 Appendix 1: New York Heart Association Classification of Heart Failure

New York Heart Association (NYHA) Classification of Heart Failure

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, rapid/irregular heartbeat (palpitation) or shortness of breath (dyspnea).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, rapid/irregular heartbeat (palpitation) or shortness of breath (dyspnea).
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, rapid/irregular heartbeat (palpitation) or shortness of breath (dyspnea).
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of fatigue, rapid/irregular heartbeat (palpitation) or shortness of breath (dyspnea) are present at rest. If any physical activity is undertaken, discomfort increases.

[Criteria Committee of the New York Heart Association 1994]

14.2 Appendix 2: Worst Itching Intensity Numerical Rating Scale (NRS)

This is a representation of the content of the instrument to be used. Please refer to the Study Reference Manual for the instrument to be administered to patients and instructions.

INSTRUCTIONS

Please indicate the intensity of the **WORST ITCHING** you experienced over the past 24 hours by marking the box with the number that best describes it. After completing the scale below, please provide your initials in the **SUBJECT INITIALS** box indicating that you completed the scale by yourself and the **DATE** and **TIME** you completed the scale.

Worst Itching Over the Past 24 Hours

Please indicate the intensity of the **WORST ITCHING** you experienced over the past 24 hours.

0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

NO ITCHING — **WORST ITCHING IMAGINABLE**

Date Completed:

☐☐ ☐☐☐ 2 0 ☐☐

D D M M M Y Y Y Y

Time:

☐☐ : ☐☐

☐ AM ☐ PM

SUBJECT INITIALS

First *Middle* *Last*

☐ ☐ ☐