A TWO-PART, MULTICENTER, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY TO EVALUATE THE SAFETY AND EFFICACY OF INTRAVENOUS CR845 IN HEMODIALYSIS PATIENTS WITH MODERATE-TO-SEVERE PRURITUS

PROTOCOL NUMBER:	CR845-CLIN2101
IND NUMBER:	123140
PROTOCOL STATUS:	Final, Version 1.0
DATE:	May 19, 2016
SPONSORED BY:	Cara Therapeutics, Inc. 4 Stamford Plaza Stamford, CT 06902 (203) 406-3700
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SIGNATURES OF AGREEMENT FOR PROTOCOL

Signature Page for Contract Research Organization.

Date: 19 MAY 2016

SPONSOR APPROVAL / SIGNATURE PAGE

I agree to oversee the conduct of the study as detailed herein and in compliance with International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP) and applicable regulatory requirements.

Date: May 19, 2016

Statement of Compliance

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP) E6 (R1) dated 10 June 1996, and the appropriate regulatory requirement(s). The Investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and Investigator's Brochure (IB). Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study, and retained according to the appropriate regulations.

The Institutional Review Board (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 the clinical site if IRB approval has been obtained. The protocol, IB, informed consent form (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. No amendments to the study protocol should be made without the prior written agreement of both the Investigator and the Sponsor, and the IRB where applicable.

The Investigator will maintain documentation of the composition of the IRB as well as all correspondence with the IRB. The Investigator will comply with local requirements for routine reporting to the IRB, as well as local and government requirements for notifying the IRB and Sponsor of any serious adverse event. The Investigator will provide Cara Therapeutics, Inc. or its designee copies of all IRB approval notices, correspondence, annual reports, and final study progress reports.

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1.0 Investigator Approval Statement

I have read and understand the protocol (CR845-CLIN2101) and the Investigator's Brochure (IB, Edition No. 7) and I agree that these documents contain all ethical, legal, and scientific information necessary to conduct this study. I will personally conduct 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 International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP) E6 (R1) dated 10 June 1996 and applicable regulatory requirements.

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

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

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

Principal Investigator: _____

Printed Name: _____

Signature: _____

Date: _____

2.0 Protocol Synopsis

STUDY TITLE	A Two-Part, Multicenter, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Intravenous CR845 in Hemodialysis Patients with Moderate-to-Severe Pruritus
PROTOCOL NUMBER	CR845-CLIN2101
PHASE OF DEVELOPMENT	2 (Part A) and 3 (Part B)
INVESTIGATIONAL PRODUCT	CR845 Solution
NAME OF ACTIVE INGREDIENT	CR845
ROUTE OF ADMINISTRATION	Intravenous (IV)
STUDY CENTERS	Part A: Up to 40 sites in United States Part B: Up to 60 sites in United States
OBJECTIVES	PART A Primary Objective • To evaluate the efficacy of 3 dose levels of IV CR845 administered after each dialysis session, compared to placebo, in reducing the intensity of itch as assessed by the change from baseline to the last week of the 8-week Treatment Period with respect to the Worst Itching Intensity Numerical Rating Scale (NRS) score of in hemodialysis patients with moderate-to-severe pruritus. Secondary Objectives • To evaluate the efficacy of 3 dose levels of IV CR845 administered after each dialysis session, compared to placebo, in improving itch-related quality-of-life measures as assessed by the Skindex-10 Scale over an 8-week Treatment Period in hemodialysis patients with moderate-to-severe pruritus. • To evaluate the safety of 3 dose levels of IV CR845 administered after each dialysis session over an 8-week Treatment Period in hemodialysis patients with moderate-to-severe pruritus. • To evaluate the pharmacokinetics (PK) of 3 dose levels of IV CR845 administered after each dialysis session over an 8-week Treatment Period in hemodialysis patients with moderate-to-severe pruritus.

OBJECTIVES	PART B One dose level will be tested in Part B after selection from the doses tested in part .A Primary Objective • To evaluate the efficacy of 1 dose level of IV CR845 administered after each dialysis session, compared to placebo, in reducing the intensity of itch as assessed by the change from baseline to the last week of the 12-week Treatment Period with respect to the Worst Itching Intensity NRS score in hemodialysis patients with moderate-to-severe pruritus. Secondary Objectives • To evaluate the efficacy of 1 dose level of IV CR845 administered after each dialysis session, compared to placebo, in improving itch-related quality-of-life measures as assessed by the Skindex-10 Scale over a 12-week Treatment Period in hemodialysis patients with moderate-to-severe pruritus. • To evaluate the safety of 1 dose level of IV CR845 administered after each dialysis session over a 12-week Treatment Period in hemodialysis patients with moderate-to-severe pruritus.
NUMBER OF PATIENTS	The planned overall (Part A + Part B) sample size for this clinical investigation is approximately 400 male and female hemodialysis patients with persistent moderate-to-severe pruritus (mean baseline 24-hour Worst Itching Intensity NRS score > 4). Part A: Approximately 160 male and female hemodialysis patients with moderate-to-severe pruritus will be randomized at approximately 40 clinical sites. Part B: Approximately 240 male and female hemodialysis patients with moderate-to-severe pruritus will be randomized at approximately 60 clinical sites.
STUDY POPULATION	**Inclusion criteria:** To be eligible for inclusion into either Part A or Part B of the study, each patient will have to fulfill 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 read, complete questionnaires, and understand the study procedures; 3. Males or females 18 years of age or older; 4. End stage renal disease (ESRD) patients who have been on hemodialysis 3 times per week for at least 3 months prior to the start of Screening; *Note 1: Patients who require an occasional additional dialysis treatment to manage fluid overload may be enrolled as long as it is anticipated that no more than 1 such treatment will be required in any given week.*

	Note 2: Patients receiving in-home hemodialysis may participate as long as they have switched to in-center hemodialysis at least 2 weeks prior to Screening and plan to remain on in-center hemodialysis for the duration of the study. 5. Female patients who are surgically sterile; or amenorrheic for at least 1 year and over the age of 55 years; or amenorrheic for at least 1 year, between the ages of 45 and 55 years, and have a serum follicle-stimulating hormone (FSH) level in the post-menopausal range at Screening; or have a negative serum pregnancy test at Screening and agree to use acceptable contraceptive measures (e.g., hormonal contraceptives, barrier with spermicide, intrauterine device, vasectomized partner, or abstinence) from the time of informed consent until the safety Follow-Up Visit or at least 7 days after the last dose, whichever is later. (Note: If the result from serum pregnancy testing at Screening is indeterminate because of possible human chorionic gonadotropin elevation secondary to ESRD unrelated to pregnancy, 1 or more serum pregnancy re-tests will be performed and reported to the Investigator prior to first dosing with the study drug to establish if a negative test result for pregnancy can be confirmed); 6. 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 has been performed ≥ 4 months prior to dosing); 7. Has a body weight of between 40.0 kg and 135.0 kg, inclusive (dry body weight); 8. Patient who self-reports experiencing pruritus during the month prior to Screening; 9. If currently using antihistamines (oral, IV, or topical), topical non-drug treatments (e.g., emollients, creams, oils), or oral or intravenous corticosteroids for itch, the current regimen (i.e., same drug, same dose, same route of administration, and same frequency) has been stable for 14 days prior to Screening and no change to the regimen is anticipated from Screening through the end of the Treatment Period; 10. If currently using opioids, gabapentin or pregabalin, the current regimen (i.e., same drug, same dose, same route of administration, and same frequency) has been stable for at least 14 days prior to Screening and no change to the regimen is anticipated from Screening through the end of the Treatment Period; 11. At least 2 single-pool Kt/V measurements ≥ 1.2, or at least 2 urea reduction ratio measurements ≥ 65%, or 1 single-pool

	Kt/V measurement ≥ 1.2 and 1 urea reduction ratio measurement ≥ 65% on different dialysis days during the 3 months period prior to Screening; 12. Patient who self-categorizes on the Patient Self-categorization of Pruritus Disease Severity questionnaire as a B or C profile at Screening; 13. At the end of the Screening Period prior to randomization: a. Patient has completed at least 4 Worst Itching Intensity NRS scores out of 7 possible daily assessments during the last 7 days prior to randomization (0-10 NRS scale where 0 = "No itching" and 10 = "Worst itching imaginable"). b. Patient has a mean baseline Worst Itching Intensity NRS score > 4, defined as the average of all non-missing scores reported during the last 7 days prior to randomization (including scores collected on Day 1, prior to randomization). **Exclusion criteria:** A patient will be excluded from either Part A or Part B of the study if any of the following criteria are met: 1. Known to be non-compliant with dialysis treatment (i.e., has missed more than 2 dialysis sessions in the past 2 months because of non-compliance); 2. Anticipated to receive a kidney transplant during the study; 3. Known history of allergic reaction to opiates, such as hives (Note: side effects related to the use of opioids, such as constipation or nausea, would not exclude patients from the study); 4. Known or suspected history of Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition-diagnosed alcohol, narcotic, or other drug abuse or dependence within 12 months prior to Screening; 5. Patient has any clinically relevant acute or chronic medical or neuropsychiatric condition including, but not limited to, severe co-morbid condition such as congestive heart failure (New York Heart Association class IV), severe mental illness, or cognitive impairment which, in the opinion of the Investigator, would pose undue risk to the patient, would impede completion of the study procedures, or would compromise the validity of the study measurements; 6. Serum alanine aminotransferase or aspartate aminotransferase greater than 2.5 times the reference upper limit of normal (ULN), or total bilirubin greater than 2 times ULN at Screening;

	7. Received another investigational drug within 30 days prior to the start of Screening or has planned to participate in another clinical trial while enrolled in this study; 8. Has pruritus probably or definitely attributed to a cause other than ESRD or its complications (e.g., patients with concomitant pruritic dermatological disease or cholestatic liver disease would be excluded). (*Note:* Patients whose pruritus is attributed to ESRD complications such as hyperparathyroidism, hyperphosphatemia, anemia, or the dialysis procedure or prescription may be enrolled); 9. Has localized itch restricted to the palms of the hands; 10. Has pruritus only during the dialysis session (by patient report); 11. Anticipated to receive opioid antagonists (e.g., naloxone, naltrexone), or opioid mixed agonist-antagonist (e.g., buprenorphine, nalbuphine) from the start of Screening through the end of the Treatment Period; 12. Used *Salvia divinorum* or Salvinorin A within 30 days prior to the start of Screening or is anticipated to use it during the study; 13. Received ultraviolet B treatment within 30 days prior to the start of Screening or is anticipated to receive such treatment during the study; 14. Participated in a previous clinical trial with CR845.
STUDY DESIGN	This is a two-part, multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of IV CR845 administered after each dialysis session. In Part A, 3 dose levels of CR845 will be evaluated relative to placebo over an 8-week Treatment Period in hemodialysis patients with moderate-to-severe pruritus. A subset of patients (approximately 10 patients per treatment group) will also be consented for the collection of blood samples for evaluating the PK profile of CR845. Based on the overall safety and efficacy profile from Part A, 1 dose of CR845 will be selected for Part B and evaluated relative to placebo over a 12-week Treatment Period in hemodialysis patients with moderate-to-severe pruritus. Part A consists of a Screening Period, an 8-week Treatment Period, an End-of-Treatment Visit (approximately 3 days after the last dose), and a Follow-Up Visit (approximately 1 week after the last dose). Part B consists of a Screening Period, a 12-week Treatment Period, an End-of-Treatment Visit (approximately 3 days after the last dose), and a Follow-Up Visit (approximately 1 week after the last dose). Part B will not be initiated until an unblinded review of the safety and efficacy data from Part A has been completed. The Screening Period will occur between 8 and 14 days prior to randomization following the signing of the informed consent form.

	Eligible patients will then be trained on completion of the 24-hour Worst Itching Intensity NRS scale and required to record their Worst Itching Intensity NRS score each day for 7 days prior to randomization. For consistency, patients will be requested to complete the NRS worksheets (either at home or in the dialysis unit, as required) at a similar time of day around the normal start time of their dialysis. During the week prior to randomization up to the first day of study drug (Day 1), patients will be trained on other PRO measures, including quality-of-life measurements. Day 1 of the Treatment Period will be defined as the day of the first dose of administration of study drug. All study visits (scheduled and unscheduled) will be conducted on dialysis days, including the end of study visit. For Part A, patients will be randomized in a 1:1:1:1 ratio to receive either CR845 1.5 mcg/kg, CR845 1.0 mcg/kg, CR845 0.5 mcg/kg, or placebo. For statistical analysis, patients will be stratified into 1 stratum according to their use or non-use of concomitant medications to treat their itch. Patients who have consented to IV blood sampling will be included in the PK sample, with approximately 10 patients per treatment arm. For Part B, patients will be randomized in a 1:1 ratio to receive either CR845 or placebo, with the dose of CR845 determined from an assessment of safety and efficacy observed in Part A. Patients enrolled in Part B will also be stratified according to their use or non-use of concomitant medications to treat their itch. Patients will be administered CR845 or matched placebo as an IV bolus immediately after the end of the dialysis session during the 8-week (Part A) or 12-week (Part B) Treatment Period so that each patient will receive CR845 3 times weekly. During the Treatment Period, PRO measurements, including Worst Itching Intensity NRS scores, will be obtained at the similar time of day (daily or bi-weekly) for a given patient, either in the dialysis unit on dialysis days or at home. Patients will report their Worst Itching Intensity NRS score over the last 24 hours daily during Screening and during the entire Treatment Period. In addition, during selected study visits, they will complete other PRO measures (Skindex-10 Scale, MOS-Sleep Scale, 5-D Itch Scale, Patient Global Impression of Worst Itch Severity, and Patient Global Impression of Change). Patients who are still in the study but miss their last on-treatment dialysis day (Week 8 for Part A; Week 12 for Part B) due to a competing medical conflict (e.g., hospitalization due to ESRD complications) will be allowed to complete the end of study visit if they return to the site within 3 days of the scheduled visit. The end of study visit will correspond to a dialysis day.

	Blood samples for inflammatory biomarkers will be collected for all randomized patients prior to dialysis on Day 1 and prior to the last dialysis of the Treatment Period. For Part A only, blood samples for evaluating the PK of CR845 will be collected in up to 40 patients (approximately 10 patients per treatment group) who have consented for this purpose, and will be collected prior to dosing on Day 1, and at pre-specified time points after the first dose of study drug. For Part B, blood samples for evaluating the PK of CR845 will be collected by sparse-sampling, using a more limited set of time points than in Part A. Vital signs and clinical laboratory tests will be monitored periodically, and adverse events and concomitant medications will be continuously recorded during the study starting at the Screening Visit until the end of the Follow-up Period. A final safety Follow-Up Visit will be conducted 7 days (+3) after the last dose of study drug.
STUDY DRUG	Study drug will be supplied in glass vials containing an extractable volume of 1.3 mL of CR845 at concentrations of 0.05 mg/mL, 0.10 mg/mL and 0.15 mg/mL in 0.04M isotonic acetate buffer, pH 4.5. The study drug will be labeled for a blinded study.
REFERENCE PRODUCT	Matching placebo (0.04M isotonic acetate buffer, pH 4.5) will be provided in glass vials containing an extractable volume of 1.3 mL.
TREATMENT REGIMENS	Part A: Four groups with a sample size of approximately 40 patients each will be administered CR845 0.5, 1, or 1.5 mcg/kg, or placebo as a single IV bolus 3 times a week immediately after each dialysis session for 8 weeks. Part B: Two groups with a sample size of approximately 120 patients each will be administered CR845 or placebo as a single IV bolus 3 times a week immediately after each dialysis session for 12 weeks. The dose of CR845 and the total sample size will be confirmed based on an unblinded review of the safety and efficacy data collected in Part A.
STUDY DURATION	Screening Period: Up to 14 days prior to Randomization Treatment Period: Part A, 8 weeks; Part B, 12 weeks Follow-Up Visit: 1 week (+3 days) Total study duration for a single patient: Part A up to 11.5 weeks; Part B, up to 15.5 weeks
STUDY ENDPOINTS	**Safety Endpoints (Parts A and B)** The safety assessments used to evaluate the overall safety of CR845 include the frequency and severity of adverse events by treatment group, physical examination, 12-lead electrocardiogram (ECG), vital signs, and clinical safety laboratory evaluations.

	Pharmacokinetic Endpoints (Part A) The PK profile of CR845 will be determined between Week 1 and Week 8, and calculation of the accumulation ratio between the first and last doses with respect to maximum concentration (C_{max}) and area under the curve (AUC) will be reported. The PK profile will be used to determine the sparse sampling schedule for Part B of the study. **Efficacy Endpoints (Parts A and B)** **Primary Efficacy Endpoint** • Change from baseline with respect to the weekly mean of the daily 24-hour Worst Itching Intensity NRS score during Week 8 (Part A) or Week 12 (Part B) of the Treatment Period **Secondary Efficacy Endpoint** • Change from baseline in itch-related quality-of-life at the end of Week 8 (Part A) or Week 12 (Part B) as assessed by the total Skindex-10 Scale score **Other Efficacy Endpoints** • **Itch-intensity measures:** o Change from baseline with respect to the weekly mean of the daily Worst Itching Intensity NRS score from Week 2 through the end of the Treatment Period (Week 8 for Part A or Week 12 for Part B) o Treatment Response, defined as the percent improvement from baseline with respect to the weekly mean of the daily Worst Itching Intensity NRS score during the last week of the Treatment Period (Week 8 for Part A or Week 12 for Part B) • **Itch-related quality-of-life measures:** o Change from baseline in itch-related quality-of-life from Week 2 through the last week of the Treatment Period (Week 8 for Part A or Week 12 for Part B) as assessed by the total Skindex-10 Scale score o Change from baseline in itch-related quality-of-life at the end of the last week of the Treatment Period (Week 8 for Part A or Week 12 for Part B), and over each week of the Treatment Period within each of the 3 domains of the Skindex-10 Scale o Change from baseline to the end of Week 8 (Part A) or Week 12 (Part B) in itch-related quality-of-life, as measured by the 5-D Itch Scale o Change from baseline to the end of Week 8 (Part A) or Week 12 (Part B) in itch-related sleep disturbance, as

	measured by the Sleep Disturbance Subscale of the Medical Outcomes Study Sleep Scale o Proportion of patients who rate their itch condition as "Very much improved" or "Much Improved", as measured by the Patient Global Impression of Change at the end of the Treatment Period (Week 8 for Part A or Week 12 for Part B) o The number and percentage of patients in each of the 5 categories of the Patient Global Impression of Worst Itch Severity at baseline, Weeks 2, 4, and 8 (Part A), or baseline, Weeks 2, 4, 8, and 12 (Part B). In addition, the proportion of patients who have a 1-point improvement or more at Week 2, 4, 8, and Week 12 (Part B only), as measured by the Patient Global Impression of Worst Itch Severity • **Missed Dialysis Visits and Incidence of Infection:** o Missed dialysis visits based on percentage of patients who missed 1 or more visits at the dialysis unit and total number of missed dialysis visits during the Treatment Period o Incidence of infection based on adverse events, hospitalizations, and/or use of antibiotics for treatment of infection related to uremic pruritus • **Inflammatory Biomarkers:** o Changes in blood levels of inflammatory biomarkers, including but not limited to hepcidin, interleukin [IL]-2, IL-6, IL-31, pre-albumin, C-reactive protein from pre-dose to the end of the Treatment Period (Week 8 for Part A or Week 12 for Part B) • **Iron Status and use of Erythropoiesis-Stimulating Agents and IV Iron** o Changes in ferritin and transferrin saturation from pre-dose to the end of the Treatment Period (Week 8 for Part A or Week 12 for Part B) o Changes in erythropoiesis-stimulating agents and/or IV iron dose, and erythropoiesis resistive index from pre-dose to the end of the Treatment Period (Week 8 for Part A or Week 12 for Part B)

INTERIM ASSESSMENT	Safety data will be reviewed on an ongoing basis by the Sponsor and a Data Monitoring Committee (DMC). No formal interim analysis of efficacy data is planned for Part A or Part B. Following completion of Part A, there will be an unblinded analysis to determine the dose of CR845 to be used in Part B. This analysis will not affect the Type I error for Part B, as it will represent the final analysis for Part A.
STATISTICAL ANALYSIS	The data from Part A of the study will be summarized and analyzed separately from the data collected in Part B of the study. **Analysis Population(s)** The Safety and Full Analysis Populations are both defined as the group of all randomized patients who received at least 1 dose of double-blind study drug. Following the intent-to-treat principle, patients in the Full Analysis Population will be analyzed according to their randomized treatment, regardless of the actual treatment received. However, patients in the Safety Analysis Population will be analyzed according to their actual treatment. The Safety Population will be used to analyze all safety endpoints while the Full Analysis Population will be used to analyze all efficacy endpoints. The Per-Protocol Population is defined as the subset of patients in the Full Analysis Population who do not have any major protocol deviations that could affect the efficacy analyses. An analysis of the primary and secondary efficacy variables for the Per-Protocol Population may be performed if more than 20% of the patients in the Full Analysis Population are excluded. The Pharmacokinetic Evaluable Population is defined as all patients who received CR845 and have sufficient plasma concentrations for PK analysis. **Safety Analyses** Safety data will be summarized descriptively. No inferential statistics are planned. Analyses of adverse event data will be summarized by Medical Dictionary for Regulatory Activities system organ class (SOC) and preferred term by treatment group, and will include summaries of treatment-emergent adverse events, serious adverse events, and adverse events resulting in study drug discontinuation. Vital signs, clinical safety laboratory, physical examination findings, and ECG data will be descriptively summarized by visit as applicable, in addition to change from baseline.

Pharmacokinetic Analyses

Plasma concentrations will be summarized descriptively and graphically by nominal time. Pharmacokinetic parameters (C_{max}, time to C_{max}, AUC, clearance, steady state volume of distribution, etc.) will be calculated based on the actual time of blood sampling. Accumulation ratios for C_{max} (R_{Cmax}) and AUC (R_{AUC}) will also be calculated. Individual plasma CR845 concentrations will be listed and plotted by patient and compared across dose groups.

Efficacy Analyses

Primary Efficacy Endpoint

The primary efficacy endpoint is defined as the change from baseline to the last week of the Treatment Period (Week 8 for Part A, and Week 12 for Part B) with respect to the weekly mean of the daily 24-hour Worst Itching Intensity NRS score. The baseline score will be defined as the average of the daily 24-hour Worst Itching Intensity NRS scores over the last 7 days prior to randomization, including pre-treatment assessments collected on Day 1.

The primary efficacy variable will be analyzed using a mixed effects model with repeated measures (MMRM). The model will contain treatment, week, and treatment-by-week interaction as fixed effects; baseline as a covariate, and patient as a random effect. For each dose group (Part A) or for the selected dose of CR845 (Part B), the treatment group difference versus placebo will be estimated as the simple contrast in the treatment effect on the last week of treatment.

An appropriate covariance matrix will be used to model the within-patient errors. The use of an unstructured covariance matrix structure as well as other structures, such as spatial patterns, that require fewer parameters (Toeplitz, autoregressive [1], or compound symmetry) will be examined. The Akaike information criterion will be used to determine the appropriate covariance matrix for the MMRM model. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom.

In the primary efficacy analysis (Part A or B), missing daily worst itching scores will not be imputed. Assuming that the data are missing at random (MAR), the estimates of the treatment differences calculated from the MMRM model described above are unbiased.

Sensitivity analyses will be conducted to evaluate the effect of the MAR assumption on the study results for Part B. Depending on the pattern and the amount of early treatment discontinuations in Part A, similar sensitivity analyses may also be performed for Part A in order to provide estimates of treatment effect under different imputation algorithms and help refine the sample size for Part B.

Secondary Efficacy Endpoint

The secondary efficacy variable is the change from baseline in the (total) Skindex-10 Scale score. An MMRM, similar to that used for the primary efficacy analysis, will be fitted to the data. The baseline value

	will be defined as the value of the Skindex-10 Scale score collected on Day 1, prior to randomization. Missing Skindex-10 Scale scores will not be imputed. Assuming that the data are MAR, the estimates of the treatment differences calculated from the MMRM models above are unbiased. *Hypothesis Testing Strategy* <u>PART A</u> The primary goal for Part A of this clinical investigation is to evaluate the efficacy of different dose levels of IV CR845 administered after each dialysis session in reducing the intensity of itch over an 8-week Treatment Period in hemodialysis patients with moderate-to-severe pruritus. Three doses will be studied (1.5 mcg/kg, 1.0 mcg/kg, and 0.5 mcg/kg), and each will be compared against placebo. One of these doses will be selected for further evaluation compared to placebo in Part B. Although a hypothesis test of each CR845 dose against placebo will be performed for each of the primary, secondary and exploratory variables, these hypothesis tests are not expected to be statistically significant based on the planned sample size of approximately 40 patients per treatment group and effect size data from previous studies of CR845 in the same population. Nevertheless, the estimates of treatment effect and p-values resulting from these hypothesis tests will be used, in addition to a review of safety data, to select the most appropriate dose for Part B. A sample size of 40 patients per group is adequate to provide an appropriate estimate of the magnitude and variability of treatment effect at each dose. <u>PART B</u> Each hypothesis test will be 2-sided and conducted at the 5% significance level. The study will be considered positive if the null hypothesis of no treatment difference is rejected in favor of the alternative that patients randomized to CR845 experience significantly less itching as measured by the change from baseline to Week 12 of the Treatment Period with respect to the weekly mean of the 24-hour Worst Itching Intensity NRS score. Further details and analysis methods are found in Section 12.0 and will be described further in the Statistical Analysis Plan.

3.0 List of Abbreviations

AUC	area under the curve
CFR	Code of Federal Regulations
C_{max}	maximum concentration
CNS	central nervous system
CRF	case report form
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
ESA	erythropoiesis-stimulating agent
ESRD	end stage renal disease
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
H	above laboratory reference range
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IL	interleukin
IND	Investigational New Drug
IRB	Institutional Review Board
IV	intravenous
IVRS/IWRS	interactive voice response system/interactive web response system
L	below laboratory reference range
MAR	missing at random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed effects model with repeated measures
MOS	Medical Outcomes Study
N	within laboratory reference range
NRS	numerical rating scale
PK	pharmacokinetic(s)
PNS	peripheral nervous system
PRO	patient reported outcome
R_{AUC}	accumulation ratio for AUC
R_{Cmax}	accumulation ratio for C_{max}
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

4.0 Introduction

4.1 Background and Rationale

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

Opioid receptors are involved in the modulation of pain signals and consist of 3 subtypes: mu, kappa, and delta. These receptor subtypes are found in the central nervous system (CNS), in peripheral nervous system (PNS) tissues such as skin and viscera, and in the immune system (see Investigator's Brochure [IB][1] for references and further details). Morphine, the most widely used opiate analgesic, acts primarily via activation of the mu opioid receptor located in the CNS and PNS, and as such, is associated with a wide array of side effects, including sedation, respiratory depression, abuse liability, and constipation. As a way to avoid these undesirable effects, CR845 was designed to activate kappa opioid receptors, located in the PNS, which are known to modulate itch, pain, and inflammatory signals without producing the side effects associated with the activation of mu opioid receptors.

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

Based on nonclinical pharmacological studies, it is anticipated that CR845 could produce a combined analgesic, anti-itch, and anti-inflammatory effect (see IB[1] for details).

Uremic pruritus is a chronic, unremitting, and highly bothersome condition in patients with chronic kidney disease which adversely affects sleep, mood, and ability to socialize[2], and is associated with increased mortality[3,4]. Large multinational studies (Dialysis Outcomes and Practice Patterns) and studies based in the United States have demonstrated that approximately 30-40% hemodialysis patients have moderate-to-severe

pruritus. There are no approved treatments for this condition in the United States, although kappa opioid agonists are known to modulate pruritus in human[5] and the mixed non-selective mu partial agonist and kappa opioid agonist nalfurafine (Remitch™) has been recently approved in Japan for the treatment of pruritus in hemodialysis patients. Thus, evaluation of the efficacy of CR845 at reducing itch in a hemodialysis population could be beneficial as it could support further clinical development for the treatment of pruritus in this population.

4.2 Clinical Experience

Overall Exposure

To date, the intravenous (IV) formulation of CR845 has been evaluated in 495 patients and healthy volunteers (231 males and 264 females) across 6 Phase 1 studies (including 1 Phase 1a/b study conducted in Japan), 3 Phase 2 studies for the relief of moderate-to-severe acute post-operative pain, and 1 Phase 2 study for the relief of moderate-to-severe pruritus in hemodialysis patients. CR845 has been evaluated both as IV bolus and 15-minute infusion of single or repeated doses ranging from 0.5 to 40 mcg/kg.

Out of the 495 subjects exposed to CR845 to date, 70 hemodialysis patients (41 males and 29 females) have received IV injection of single or repeated CR845 doses (for up to 2 weeks) ranging from 0.5 to 6 mcg/kg across one Phase 1 study and one Phase 2 safety and efficacy study.

Safety in Hemodialysis Patients

A review of the aggregate safety data for hemodialysis patients 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 a period of up to 2 weeks at IV doses ranging from 0.5 mcg/kg to 6 mcg/kg. Although patients exposed to CR845 reported more adverse events compared to placebo patients, most were mild or moderate in nature.

Generally mild, transient paresthesias (facial tingling) and/or hypoesthesias (in different anatomic locations), mostly on the first day of dosing, as well as headache, dizziness, and somnolence, were the most frequently reported adverse events associated with CR845

administration. However, psychiatric side effects (e.g., dysphoria and hallucinations) commonly associated with centrally-acting kappa opioids were not reported in patients exposed to CR845. Other common mu-opioid side effects such as vomiting, constipation, and euphoria were also not observed; nausea occurred with a frequency similar to that in the placebo group. Consistent with its lack of affinity for the mu-opioid receptor, CR845 did not cause respiratory depression, reduction in oxygen saturation, or decreased blood pressure.

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 signs. 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 mu-opioid agonists.

Adverse event summary tables can be found in the IB[1] with further details of the safety profile of CR845 established to date in this population.

Efficacy of CR845 in Hemodialysis Patients with Uremic Pruritus

The efficacy of CR845 in uremic pruritus was evaluated in a Phase 2, randomized, double-blind, placebo-controlled trial (CR845-CLIN2005, Part B) that 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 the quality-of-life related to itching (Skindex-10 Scale) (see IB[1] 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 on non-dialysis 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.

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 (Study CR845-CLIN1005) such that plasma levels of CR845 remain relatively constant until cleared during dialysis in hemodialysis patients (Study CR845-CLIN1003 and CR845-CLIN2005), with half-life ranging 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 pharmacokinetic (PK) profile, it was established that 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 (C_{max}) and area under the curve (AUC), and minimum to no accumulation with repeat doses due to clearance of the drug by hemodialysis (see IB[1] for details).

4.3 Summary of Potential Risks and Benefits

The potential benefit of CR845 in alleviating the symptoms of uremic pruritus is predicated on its pharmacological class and evidence of its effectiveness in multiple animal models of pruritus and in one Phase 2 clinical trial with hemodialysis patients experiencing moderate-to-severe pruritus (CR845-CLIN2005, Part B)

In humans with normal renal function, CR845 has aquaretic effects which can result in dehydration and associated symptoms (e.g., dizziness, tachycardia) and hypernatremia if the fluid balance is not managed properly. However, these effects appear to be absent in the dialysis population, many of whom are anuric and all of whom have few functioning nephrons.

Potential risks of CR845 include the possible occurrence of adverse events of mild somnolence and transient mild or moderate dizziness following the first dose, which have been reported in 3-6% of patients at doses planned for this trial. Therefore, as a precaution, investigators should advise patients not to drive or operate machinery on Day 1 following the first dose, until it is determined that the patient does not experience these possible adverse events. While it has been demonstrated that CR845 has substantially less access to the CNS than previously tested kappa opioid agonists, adverse neurobehavioral effects of CR845 could still be considered a possibility (e.g., hypothetically, in patients with impaired blood-brain barrier functioning).

A more detailed summary of the potential risks of CR845 is provided in the IB.[1] The Investigator must become familiar with all sections of the current IB for CR845 before the start of the study.

5.0 Safety Monitoring Plan

The safety monitoring plan is intended to minimize risk for patients participating in this study. General safety monitoring will include assessment of adverse events, measurements of serum chemistry, hematology, vital signs, 12-lead electrocardiograms (ECGs), and physical examinations. Following completion of study drug treatment, patients will return for a safety Follow-Up Visit. Based on the safety profile of CR845 observed in a 2-week treatment study, this study aims to further evaluate safety as well as efficacy during treatment with CR845 for 8 weeks (Part A) and 12 weeks (Part B). The doses selected for this study include the 1 mcg/kg dose, which was found to be effective and to have a good safety profile, a lower dose (0.5 mcg/kg), and a higher dose (1.5 mcg/kg), which has not been previously studied, but is well within the range of doses previously studied in hemodialysis patients (0.5 mcg/kg to 6 mcg/kg) (See Section 9.2.2.). Frequent study visits (3 times/week) permit close safety monitoring of patients. Because CR845 is effectively cleared by hemodialysis (CR845-CLIN1003 and CR845-CLIN2005), this procedure enables removal of the drug in situations of unintentional overdose or if a patient is experiencing a severe or serious adverse event (SAE) that, in the opinion of the Investigator, could possibly, probably or definitely be drug-related, such that removal of the drug could potentially be of benefit to the patient.

6.0 Objectives

6.1 Part A

Primary Objective

The primary objective is to evaluate the efficacy of 3 dose levels of IV CR845 administered after each dialysis session, compared to placebo, in reducing the intensity of itch as assessed by the change from baseline to the last week of the 8-week Treatment Period with respect to the Worst Itching Intensity Numerical Rating Scale (NRS) score of in hemodialysis patients with moderate-to-severe pruritus.

Secondary Objectives

The secondary objectives are:

- To evaluate the efficacy of 3 dose levels of IV CR845 administered after each dialysis session, compared to placebo, in improving itch-related quality-of-life measures as assessed by the Skindex-10 Scale over an 8-week Treatment Period in hemodialysis patients with moderate-to-severe pruritus.
- To evaluate the safety of 3 dose levels of IV CR845 administered after each dialysis session over an 8-week Treatment Period in hemodialysis patients with moderate-to-severe pruritus.
- To evaluate the PK of 3 dose levels of IV CR845 administered after each dialysis session over an 8-week Treatment Period in hemodialysis patients with moderate-to-severe pruritus.

6.2 Part B

One dose level will be tested in Part B after selection from the doses tested in part A and which will be the dose which represents best efficacy and safety

Primary Objective

The primary objective is to evaluate the efficacy of 1 dose level of IV CR845 administered after each dialysis session, compared to placebo, in reducing the intensity of itch as assessed by the change from baseline to the last week of the 12-week Treatment

Period with respect to the Worst Itching Intensity NRS score in hemodialysis patients with moderate-to-severe pruritus.

Secondary Objectives

The secondary objectives are:

- To evaluate the efficacy of 1 dose level of IV CR845 administered after each dialysis session, compared to placebo, in improving itch-related quality-of-life measures as assessed by the Skindex-10 Scale over a 12-week Treatment Period in hemodialysis patients with moderate-to-severe pruritus.
- To evaluate the safety of 1 dose level of IV CR845 administered after each dialysis session over a 12-week Treatment Period in hemodialysis patients with moderate-to-severe pruritus.

7.0 Investigational Plan

This is a two-part, multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of IV CR845 administered after each dialysis session. In Part A, 3 dose levels of CR845 will be evaluated relative to placebo over an 8-week Treatment Period in hemodialysis patients with moderate-to-severe pruritus. A subset of patients (approximately 10 patients per treatment group) will also be consented for the collection of blood samples for evaluating the PK profile of CR845. Based on the overall safety and efficacy profile of the 3 doses in Part A, 1 dose of CR845 will be selected for further evaluation relative to placebo over a 12-week Treatment Period in hemodialysis patients with moderate-to-severe pruritus in Part B.

7.1 Study Design and Rationale

The present study is designed to further evaluate the efficacy and safety of IV CR845 in end stage renal disease (ESRD) patients on hemodialysis with uremic pruritus. A randomized, double-blind design was chosen to minimize bias. In Part A, an 8-week duration was selected to demonstrate durability of the efficacy observed in a prior 2-week treatment trial and to further evaluate safety following a longer exposure. The primary efficacy endpoint is the Worst Itching Intensity NRS scale, which measures itching intensity over 24 hours. Although prior studies [Mathur 2010[6]; CR845-CLIN2005] utilized separate measures of the worst itching intensity during the daytime and nighttime, based on the similarity of the daytime and nighttime scores in the prior study CR845-CLIN2005, only a single measurement to describe itching during the entire 24-hour period will be used in this study. A 24-hour recall period is a standard recall period for the evaluation of other chronic conditions such as chronic pain or osteoarthritis. Prior to the initiation of this clinical trial, Cara will conduct a study to confirm the appropriateness of a 24-hour recall period in hemodialysis patients. Daily Worst Itching Intensity NRS scores will be collected to evaluate pruritus efficacy on both dialysis and non-dialysis days as was done in the prior study CR845-CLIN2005.

Part A consists of a Screening Period, an 8-week Treatment Period, an End-of-Treatment Visit (approximately 3 days after the last dose), and a Follow-Up Visit (approximately 1 week after the last dose).

Part B consists of a Screening Period, a 12-week Treatment Period, an End-of-Treatment Visit (approximately 3 days after the last dose), and a Follow-Up Visit (approximately

1 week after the last dose). Part B will not be initiated until an unblinded review of the safety and efficacy data from Part A has been completed.

The Screening Period will occur within 14 days prior to randomization following the signing of the informed consent form (ICF).

Eligible patients will then be trained on completion of the 24-hour Worst Itching Intensity NRS scale and required to record their Worst Itching Intensity NRS scale each day for 7 days prior to randomization. For consistency, patients will be requested to complete the NRS worksheets (either at home or in the dialysis unit, as required) at a similar time of day around the normal start time of their dialysis. During the week prior to randomization up to the first day of study drug (Day 1), patients will be trained on other PRO measures, including quality-of-life measurements.

Day 1 of the Treatment Period will be defined as the day the first dose of administration of study drug. Study weeks will begin on the same day of the week as randomization (e.g., for a patient randomized on a Tuesday, all study weeks will start on Tuesday and end on Monday).

All study visits (scheduled and unscheduled) will be conducted on dialysis days, including the end of study visit.

For Part A, patients will be randomized in a 1:1:1:1 ratio to receive either CR845 1.5 mcg/kg, CR845 1.0 mcg/kg, CR845 0.5 mcg/kg, or placebo. For statistical analysis, patients will be stratified into 1 strata according to their use or non-use of concomitant medications to treat their itch. Patients who have consented to IV blood sampling will be included in the PK sample, with approximately 10 patients per treatment arm. For Part B, patients will be randomized in a 1:1 ratio to receive either CR845 or placebo, with the dose of CR845 determined from an assessment of safety and efficacy observed in Part A. Patients enrolled in Part B will also be stratified according to their use or non-use of concomitant medications to treat their itch.

Patients will be administered CR845 or matched placebo as an IV bolus immediately after the end of the dialysis session during the 8-week (Part A) or 12-week (Part B) Treatment Period so that each patient will receive CR845 3 times weekly. Patients receiving a 4th dialysis treatment during a given week (e.g., for fluid overload) should receive an extra dose of CR845 following dialysis after this treatment. During the

Treatment Period, PRO measurements, including Worst Itching Intensity NRS scores, will be obtained at the similar time of day (daily or bi-weekly) for a given patient, either in the dialysis unit on dialysis days or at home.

Patients will report their Worst Itching Intensity NRS score over the last 24 hours daily during Screening and during the entire Treatment Period. In addition, during selected study visits, they will complete other PRO measures (Skindex-10 Scale, MOS-Sleep Scale, 5-D Itch Scale, Patient Global Impression of Worst Itch Severity, and Patient Global Impression of Change).

Patients who are still in the study but miss their last on-treatment dialysis day (Week 8 for Part A; Week 12 for Part B) due to a competing medical conflict (e.g., hospitalization due to ESRD complications) will be allowed to complete the end of study visit if they return to the site within 3 days of the scheduled visit. The end of study visit will correspond to a dialysis day.

Blood samples for inflammatory biomarkers will be collected for all randomized patients prior to dialysis on Day 1 and prior to the last dialysis of the Treatment Period.

For Part A, blood samples for evaluating the PK of CR845 will be collected in up to 40 patients (approximately 10 patients per treatment group) who have consented for this purpose, and will be collected prior to dosing on Day 1, and at pre-specified time points after the first dose of study drug. For Part B, blood samples for evaluating the PK of CR845 will be collected by sparse-sampling, using a more limited set of time points than in Part A.

Vital signs and clinical laboratory tests will be monitored periodically, and adverse events and concomitant medications will be continuously recorded during the study starting at the Screening Visit until the end of the Follow-up Period.

A final safety Follow-Up Visit will be conducted 7 days (+3) after the last dose of study drug.

A review of the safety data for each part of this study will be conducted on an ongoing basis by the Sponsor and an independent Data Monitoring Committee (DMC).

7.2 Number of Patients and Sites

The planned sample size for this clinical investigation is approximately 400 male and female hemodialysis patients with persistent moderate-to-severe pruritus (mean baseline Worst Itching Intensity NRS score > 4).

Part A: Approximately 160 male and female hemodialysis patients with moderate-to-severe pruritus will be randomized at approximately 40 clinical sites. For Part A, a subset of up to 40 patients (10 per treatment group) will be consented for the collection of blood samples for evaluating the PK profile of CR845.

Part B: Approximately 240 male and female hemodialysis patients with moderate-to-severe pruritus will be randomized at approximately 60 clinical sites.

7.3 Randomization

Before the start of the study, computer-generated randomization schedules will be prepared. Randomization will be performed using an Interactive Voice or Web Response System (IVRS/IWRS). For Part A, patients will be randomized in a 1:1:1:1 ratio to receive CR845 1.5 mcg/kg, CR845 1.0 mcg/kg, CR845 0.5 mcg/kg, or placebo. Patients will be stratified according to their use or non-use (i.e., 2 strata will be defined) of concomitant medications to treat their itch and their inclusion in the PK sample of approximately 10 patients per treatment arm. For Part B, patients will be randomized in a 1:1 ratio to receive either CR845 or placebo, with the dose of CR845 determined based on safety and efficacy determined in Part A. Patients enrolled in Part B will also be stratified according to their use or non-use of concomitant medications to treat their itch. For both Part A and B, patients will be categorized as "using anti-pruritic medications" if they have used $\geq$1 dose of potentially anti-pruritic medications used to treat their uremic pruritus during the week prior to Randomization (e.g. antihistamine (H1), pregabalin, gabapentin, nalbuphine, naltrexone, corticosteroids, or buprenorphine).

7.4 Blinding

Patients, Investigators, study staff, and the Sponsor will be blinded to treatment assignment.

For medically urgent or emergent situations that necessitate knowledge of treatment assignment for patient management, the blind may be broken via the IVRS/IWRS. The Medical Monitor must be contacted prior to breaking the blind, whenever possible; however, in all cases, the Medical Monitor must be notified within 24 hours of the blind being broken.

7.5 Endpoints

7.5.1 Safety Endpoints

The safety assessments used to evaluate the overall safety of CR845 include the frequency and severity of adverse events by treatment group, physical examination, 12-lead ECG, vital signs, and clinical safety laboratory evaluations.

7.5.2 Pharmacokinetic Endpoints

For Part A, the PK profile of CR845 will be determined between Week 1 and Week 8, and calculation of the accumulation ratio between the first and last doses with respect to C_{max} and AUC will be reported. The PK profile from Part A will be used to determine the sparse sampling schedule for Part B of the study.

Details of the PK analysis will be provided in a separate PK analysis plan.

7.5.3 Primary Efficacy Endpoint

The primary efficacy endpoint will be change from baseline with respect to the weekly mean of the daily 24-hour Worst Itching Intensity NRS score during Week 8 (Part A) or Week 12 (Part B) of the Treatment Period.

7.5.4 Secondary Efficacy Endpoint

The secondary efficacy endpoint will be change from baseline in itch-related quality-of-life at the end of Week 8 (Part A) or Week 12 (Part B) as assessed by the total Skindex-10 Scale score.

7.5.5 Other Efficacy Endpoints

Itch-related and quality-of-life endpoints include the following:

Itch intensity:

- Change from baseline with respect to the weekly mean of the daily Worst Itching Intensity NRS score from Week 2 through the end of the Treatment Period (Week 8 for Part A or Week 12 for Part B)

- Treatment Response, defined as the percent improvement from baseline with respect to the weekly mean of the daily Worst Itching Intensity NRS score during the last week of the Treatment Period (Week 8 for Part A or Week 12 for Part B)

Itch-related quality-of-life:

- Change from baseline in itch-related quality-of-life from Week 2 through the last week of the Treatment Period (Week 8 for Part A or Week 12 for Part B) as assessed by the total Skindex-10 Scale score
- Change from baseline in itch-related quality-of-life at the end of the last week of the Treatment Period (Week 8 for Part A or Week 12 for Part B), and over each week of the Treatment Period within each of the 3 domains of the Skindex-10 Scale
- Change from baseline to the end of Week 8 (Part A) or Week 12 (Part B) in itch-related quality-of-life, as measured by the 5-D Itch Scale
- Change from baseline to the end of Week 8 (Part A) or Week 12 (Part B) in itch-related sleep disturbance, as measured by the Sleep Disturbance Subscale of the MOS Sleep Scale
- Proportion of patients who rate their itch condition as “Very much improved” or “Much Improved”, as measured by the Patient Global Impression of Change at the end of the Treatment Period (Week 8 for Part A or Week 12 for Part B)
- Proportion of patients who have a 1-point improvement or more at Week 2, 4, 8, and Week 12 (Part B only), as measured by the Patient Global Impression of Worst Itch Severity

Missed dialysis visits and incidence of infection include the following:

- Missed dialysis visits based on percentage of patients who missed 1 or more visits at the dialysis unit and total number of missed dialysis visits during the Treatment Period

- Incidence of infection based on adverse events, hospitalizations, and/or use of antibiotics for treatment of infection related to uremic pruritus

Inflammatory biomarkers include:

- Changes in blood levels of inflammatory biomarkers, including but not limited to hepcidin, interleukin [IL]-2, IL-6, IL-31, pre-albumin and C-reactive protein from pre-dose to the end of the Treatment Period (Week 8 for Part A or Week 12 for Part B)

Iron Status and use of Erythropoiesis-stimulating agents and IV iron include:

- Changes in ferritin and transferrin saturation from pre-dose to the end of the Treatment Period (Week 8 for Part A or Week 12 for Part B)
- Changes in ESAs and/or IV iron dose, and erythropoiesis resistive index from pre-dose to the end of the Treatment Period (Week 8 for Part A or Week 12 for Part B)

The baseline value of the primary efficacy endpoint will be calculated using all the 24-hour Worst Itching Intensity NRS scores reported during the last 7 days prior to randomization, including Day 1 scores collected prior to the administration of the first dose of double-blind study drug. The baselines for other PRO measures are the pre-dose assessments collected on Day 1.

7.6 Duration of Treatment

For Part A, the duration of treatment for each individual patient is expected to be 8 weeks, for a total of approximately 24 doses of study drug (3 doses per week) administered immediately following each dialysis session. The overall study duration for each individual patient is expected to be up to 11.5 weeks.

For Part B, the duration of treatment for each individual patient is expected to be 12 weeks, for a total of approximately 36 doses of study drug (3 doses per week) administered immediately following each dialysis session. The overall study duration for each individual patient is expected to be up to 15.5 weeks.

7.7 Selection of the Patient Population

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

Patients will be screened for inclusion in the study before enrollment, randomization, and dosing. All inclusion/exclusion criteria must be met before a patient is enrolled.

Rescreening will be considered on an individual subject basis and must first be approved by the Sponsor or Medical Monitor.

The Sponsor reserves the right to grant waivers for certain subjects who may not meet all inclusion and exclusion criteria. Waivers granted must first be approved by the Medical Monitor. Documentation of all waivers and rationale will be included in the clinical study report.

7.7.1 Inclusion Criteria

To be eligible for inclusion into either Part A or Part B of the study, each patient will have to fulfill 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 read, complete questionnaires, and understand the study procedures;
3. Males or females 18 years of age or older;
4. ESRD patients who have been on hemodialysis 3 times per week for at least 3 months prior to the start of Screening;

   Note 1: Patients who require an occasional additional dialysis treatment to manage fluid overload may be enrolled as long as it is anticipated that no more than 1 such treatment will be required in any given week.

   Note 2: Patients receiving in-home hemodialysis may participate as long as they have switched to in-center hemodialysis at least 2 weeks prior to Screening and plan to remain on in-center hemodialysis for the duration of the study.
5. Female patients who are surgically sterile; or amenorrheic for at least 1 year and over the age of 55 years; or amenorrheic for at least 1 year, between the ages of 45 and 55 years, and have a serum follicle-stimulating hormone (FSH) level in the post-menopausal range at Screening; or have a negative serum pregnancy test at Screening and agree to use acceptable contraceptive measures (e.g., hormonal contraceptives, barrier with spermicide, intrauterine device, vasectomized partner, or abstinence) from the time of informed consent until the safety Follow-Up Visit or at least 7 days after the last dose, whichever is later. (Note: If the result from serum pregnancy testing at Screening is indeterminate because of possible human chorionic gonadotropin elevation secondary to ESRD unrelated to pregnancy, 1 or more serum pregnancy re-tests will be performed and reported to the Investigator prior to first dosing with the study drug to establish if a negative test result for pregnancy can be confirmed);
6. 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 has been performed ≥ 4 months prior to dosing);

7. Has a body weight of between 40.0 kg and 135.0 kg, inclusive (dry body weight);
8. Patient who self-reports experiencing pruritus during the month prior to Screening;
9. If currently using antihistamines (oral, IV, or topical), topical non-drug treatments (e.g., emollients, creams, oils), or oral or intravenous corticosteroids for itch, the current regimen (i.e., same drug, same dose, same route of administration, and same frequency) has been stable for 14 days prior to Screening and no change to the regimen is anticipated from Screening through the end of the Treatment Period;
10. If currently using opioids, gabapentin or pregabalin, the current regimen (i.e., same drug, same dose, same route of administration, and same frequency) has been stable for at least 14 days prior to Screening and no change to the regimen is anticipated from Screening through the end of the Treatment Period;
11. At least 2 single-pool Kt/V measurements ≥ 1.2, or at least 2 urea reduction ratio measurements ≥ 65%, or 1 single-pool Kt/V measurement ≥ 1.2 and 1 urea reduction ratio measurement ≥ 65% on different dialysis days during the 3 months period prior to Screening;
12. Patient who self-categorizes on the Patient Self-categorization of Pruritus Disease Severity questionnaire as a B or C profile at Screening;
13. At the end of the Screening Period prior to randomization;
    a. Patient has completed at least 4 Worst Itching Intensity NRS scores out of 7 possible daily assessments during the last 7 days prior to randomization (0-10 NRS scale where 0 = "No itch at all" and 10 = "Worst itching imaginable");
    b. Patient has a mean baseline Worst Itching Intensity NRS score > 4, defined as the average of all non-missing scores reported during the last 7 days prior to randomization (including scores collected on Day 1, prior to randomization).

7.7.2 Exclusion Criteria

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

1. Known to be non-compliant with dialysis treatment (i.e., has missed more than 2 dialysis sessions in the past 2 months because of non-compliance);
2. Anticipated to receive a kidney transplant during the study;
3. Known history of allergic reaction to opiates, such as hives (Note: side effects related to the use of opioids, such as constipation or nausea, would not exclude patients from the study);

4. Known or suspected history of Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition-diagnosed alcohol, narcotic, or other drug abuse or dependence within 12 months prior to Screening;
5. Patient has any clinically relevant acute or chronic medical or neuropsychiatric condition including, but not limited to, severe co-morbid condition such as congestive heart failure (New York Heart Association class IV), severe mental illness, or cognitive impairment which, in the opinion of the Investigator, would pose undue risk to the patient, would impede completion of the study procedures, or would compromise the validity of the study measurements;
6. Serum alanine aminotransferase or aspartate aminotransferase greater than 2.5 times the reference upper limit of normal (ULN), or total bilirubin greater than 2 times ULN at Screening;
7. Received another investigational drug within 30 days prior to the start of Screening or has planned to participate in another clinical trial while enrolled in this study;
8. Has pruritus probably or definitely attributed to a cause other than ESRD or its complications (e.g., patients with concomitant pruritic dermatological disease or cholestatic liver disease would be excluded). (*Note:* Patients whose pruritus is attributed to ESRD complications such as hyperparathyroidism, hyperphosphatemia, anemia, or the dialysis procedure or prescription may be enrolled);
9. Has localized itch restricted to the palms of the hands;
10. Has pruritus only during the dialysis session (by patient report);
11. Anticipated to receive opioid antagonists (e.g., naloxone, naltrexone), or opioid mixed agonist-antagonist (e.g., buprenorphine, nalbuphine) from the start of Screening through the end of the Treatment Period;
12. Used *Salvia divinorum* or Salvinorin A within 30 days prior to the start of Screening or is anticipated to use it during the study;
13. Received ultraviolet B treatment within 30 days prior to the start of Screening or anticipated to receive such treatment during the study;
14. Participated in a previous clinical trial with CR845.

7.8 Withdrawal of Patients from Therapy or Assessment

A patient may voluntarily withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The Investigator or Sponsor may withdraw the patient at any time for any reason (e.g., in the interest of patient safety). Additional reasons for premature discontinuation of study drug may include adverse events and major non-compliance with study procedures as described below. The withdrawal of a patient from study drug by the Investigator should

be discussed with the Medical Monitor before the patient stops study drug, whenever possible.

If study drug is discontinued, regardless of the reason, an Early Termination Visit should be completed immediately or within no more than 2 to 3 days after the last dose of study drug or, if not feasible during that timeframe, then as soon as feasible afterwards. The reason(s) for termination and date of stopping study drug must be recorded on the case report form (CRF) and source documents. Patients prematurely discontinuing study drug are required to undergo the final safety Follow-Up Visit, if possible. Even if this visit is missed, adverse events starting within 7 days following the last dose of study drug must be reported.

Although a patient will not be obliged to give a reason for withdrawing prematurely, the Investigator is asked to make a reasonable effort to obtain the reason while fully respecting the patient's rights. The reason for premature discontinuation from the study must be recorded in the patient's source document and on the CRF whenever possible. Reasons for patient discontinuation from the study may include but are not limited to:

- Major protocol violation
- Adverse event
- Lack of therapeutic efficacy
- Patient non-compliance
- Withdrawal of consent by patient for any or all study procedures
- Sponsor decision to terminate the study early.

If a patient withdraws or is withdrawn for more than 1 reason, each reason should be documented in the source document. However, only the primary reason will be captured on the CRF.

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.

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

7.9 Contraception, Pregnancy, and Sperm Donation

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

- surgically sterile (i.e., tubal ligation, bilateral oophorectomy, and/or hysterectomy) or
- over 55 years of age and have not had a menstrual period in at least 1 year or
- between 45 and 55 years of age and have not had a menstrual period in at least 1 year and have serum FSH level in the post-menopausal range.

All women of childbearing potential should be counseled on the need to practice adequate birth control once they have consented to participate in the study for the duration of the study, from Screening until 7 days after the last treatment, and on the importance of avoiding pregnancy.

Medically acceptable methods of birth control are methods with a low failure rate of less than 1% per year, which include hormonal contraceptives for at least 1 cycle of treatment before trial enrollment or an intra-uterine device, or double barrier method (male or female condom, diaphragm).

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

If a patient becomes pregnant during or after exposure to a study drug received in this study within 7 days, 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 pregnancy exposures in the clinical trial. 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 is 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 notification form will be completed.

Male patients must agree not to donate sperm from study drug administration on Day 1 until 7 days after dosing, and must 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 has been performed 4 months or more prior to dosing.

7.10 Data Monitoring Committee

An ongoing review of the cumulative safety data for this study will be conducted by an external DMC for both Part A and Part B of this study. The DMC will be comprised of approximately 3 to 5 voting members with expertise in areas relevant to the clinical program.

This DMC will meet periodically to review safety data as the study progresses and, based upon the findings, will make recommendations about the conduct of the study.

The operation of the DMC will be governed by a charter that will describe the groups' frequency of meeting, procedures (including, but not limited to, periodic safety monitoring) and requirements for reporting its observations to the Sponsor.

8.0 Study Procedures

8.1 Screening (Part A and Part B)

The patient must be screened within 14 days and no less than 7 days prior to the beginning of the Treatment Period.

Screening	
Sign ICF	Written consent form needs to be signed prior to the initiation of the screening visit.
Obtain patient identification number	Register the patient in the electronic data capture system to obtain an identification number
Inclusion/exclusion criteria review	Confirm eligibility for the study
Obtain and record medical and medication history	Events occurring prior to the signature of the ICF will be reported as medical history.
Record procedural data for dialysis (including ESA and IV Iron Use)	Record drug name, date, type, dose, and unit for each individual time ESA or IV Iron was administered in the last 3 months prior to Screening.
Measure height	Height will be reported with the patient's shoes removed.
Record estimated dry body weight	Target post-dialysis weight
Perform physical examination	At minimum, an examination of the heart, lungs, abdomen, extremities, neurological system, and vascular system
Measure vital signs	Includes blood pressure, heart rate, and body temperature. Obtain prior to start of dialysis.
Obtain blood for central laboratory tests	Chemistry and hematology. Obtain prior to the start of dialysis.
Obtain blood for central laboratory pregnancy test and FSH	Obtain pregnancy test on women of childbearing potential. FSH is needed only in women who have been amenorrheic for at least 1 year and are between 45 and 55 years of age.
Patient questionnaire training session	Patient training on the Worst Itching Intensity NRS. Skindex-10 Scale, MOS Sleep Scale, 5-D Itch Scale, and Patient Global Impression of Worst Itch Severity training (complete in the dialysis unit) will be done at any time during the week prior to randomization (Days -7 to -1).
Have patient complete the Patient Self-categorization of Pruritus Disease Severity	To be completed in the dialysis unit
Obtain 12-lead ECG	Obtain prior to the start of dialysis

Give patient NRS worksheets to take home and collect NRS worksheets completed at home at each dialysis session for 7 days. In addition have patient complete NRS worksheet at the dialysis unit on the day of their dialysis (prior or during dialysis) until the day the of randomization.	In order to establish a baseline itch intensity, NRS worksheets will be completed by the patient daily at home on non-dialysis days, and at the dialysis center on dialysis days for 7 days prior to randomization and after patient's eligibility to the study has been confirmed. For consistency, patients will be requested to complete the NRS worksheets (either at home or in the dialysis unit) at a similar time of day around the normal start time of their dialysis. The patient will be instructed to bring the completed worksheets from home to the dialysis unit at each dialysis session for collection. It is imperative that worksheets be collected from the patients and reviewed by the study staff on the days indicated, both to help remind the patients to complete them and to provide additional training, if initial returned worksheets were not completed according to instructions.

8.2 Treatment Period

All questionnaires must be completed in strict adherence to the Patient Reported Outcomes Instructions (as per Study Reference Manual).

8.2.1 Week 1 (Part A and Part B)

8.2.1.1 Day 1 (Monday or Tuesday)

Day 1 (Monday or Tuesday)	
Update medical history and prior medications, if applicable	
Collect remaining patient NRS worksheets completed at home	Worksheet completed by the patient at home and brought to the dialysis unit
Obtain Worst Itching Intensity NRS score	This score will be recorded at the dialysis unit and will reflect the worst itching on the last day of the screening period, prior to initiating treatment
Confirm inclusion/exclusion criteria	Enter Worst Itching Intensity NRS scores into IVRS/IWRS to confirm eligibility for Inclusion criterion #13
Record estimated dry weight	
Perform randomization	Via IVRS/IWRS
After Randomization, Prior to the Start of Dialysis	
Measure vital signs	Includes blood pressure, heart rate, and body temperature.
Perform 12-lead ECG	
Obtain blood for central laboratory tests	Chemistry and hematology
Obtain blood for inflammatory biomarker	
Dialysis The dialysis prescription should be kept constant throughout the study, unless absolutely necessary for patient safety.	
Anytime Prior to or During Dialysis	
Re-train patient on questionnaires as needed and have Patient complete the questionnaires required for that day (completion in the dialysis unit)	Skindex-10 Scale, MOS Sleep Scale , 5-D Itch Scale, and Patient Global Impression of Worst Itch Severity.
Record procedural data for dialysis	Start and stop times, net ultrafiltration, access changes, dialysis bath sodium concentration, IV iron, and ESA usage
Give patient NRS worksheets to take home	Review instructions for completion of worksheets Remind patient to bring back completed worksheets to each dialysis session
Record adverse events and prior medications	
After Dialysis	
Study drug administration	Administer an IV bolus of study drug within 15 minutes following the end of the dialysis (i.e., following return of blood to the patient)
Measure post-dialysis body weight	
Record concomitant medication if applicable	

For a subset of patients in Part A, blood samples for PK analysis will be collected from the predialyzer (arterial) line at the Week 1, Day 1 and Day 2 time points listed in the Pharmacokinetic Sampling Schedule (Appendix II, Section 18.2).

8.2.1.2 Days 3 (Wednesday or Thursday) and 5 (Friday or Saturday)

Days 3 and 5	
Anytime During the Visit prior to Study Drug Administration	
Collect and review NRS worksheets completed at home	
Give patient new NRS worksheets to take home	Review instructions for completion of worksheets Remind patient to bring back completed worksheets to each dialysis session
Patient questionnaires	Worst Itching Intensity NRS score (complete in the dialysis unit)
Anytime During the Visit	
Record adverse events	
Anytime During Dialysis The dialysis prescription should be kept constant throughout the study, unless absolutely necessary for patient safety.	
Record procedural data	Start and stop times, net ultrafiltration, access changes, dialysis bath sodium concentration, IV iron, and ESA usage
Study Drug Administration	
Study drug administration	Administer an IV bolus of study drug within 15 minutes following the end of the dialysis (i.e., following return of blood to the patient)

For a subset of patients in Part A, blood samples for PK analysis will be collected from the predialyzer (arterial) line at the Day 3 time points listed in the Pharmacokinetic Sampling Schedule (Appendix II, Section 18.2).

8.2.2 Weeks 2 through 8 (Part A and Part B)

8.2.2.1 Days 8, 15, 22, 29, 36, 43 and 50 (Monday or Tuesday)

Days 8, 15, 22, 29, 36, 43, and 50	
Anytime During the Visit prior to Study Drug Administration	
Collect and review NRS worksheets completed at home	
Give patient new NRS worksheets to take home	Review instructions for completion of worksheets Remind patient to bring back completed worksheets to each dialysis session
Patient questionnaires	Worst Itching Intensity NRS score for the past 24 hours (complete at each visit to the dialysis unit)
	Skindex-10 Scale and 5-D Itch Scale (Days 15, 29, and 43)
	MOS Sleep Scale (Days 22 and 50)
	Patient Global Impression of Worst Itch Severity (Days 8, 22, and 50)
Anytime During the Visit	
Record adverse events and concomitant medications	
Prior to the Start of Dialysis	
Measure vital signs (Days 15 and 29 only)	
Obtain blood for central laboratory tests (Days 15, 29, and 43 only)	
Collect 12-lead ECG (Day 29 only)	
Anytime During Dialysis The dialysis prescription should be kept constant throughout the study, unless absolutely necessary for patient safety.	
Record procedural data	Start and stop times, net ultrafiltration, access changes, dialysis bath sodium concentration, IV iron, and ESA usage
After Dialysis	
Study drug administration	Administer an IV bolus of study drug within 15 minutes following the end of the dialysis (i.e., following return of blood to the patient)

For a subset of patients in Part A, blood samples for PK analysis will be collected from the predialyzer (arterial) line at the time points listed in the Pharmacokinetic Sampling Schedule (Appendix II, Section 18.2) (i.e., Week 2, Day 8; Week 4, Day22; Week 6, Day 36; Week 8, Day 50) .

8.2.2.2 Days 10, 17, 24, 31, 38, 45, and 52 (Wednesday or Thursday) and Days 12, 19, 26, 33, 40, 47, and 54 (Friday or Saturday)

Days 10, 17, 24, 31, 38, 45, and 52 (Wednesday or Thursday) and Days 12, 19, 26, 33, 40, 47, and 54 (Friday or Saturday)	
Anytime During the Visit prior to Study Drug Administration	
Collect and review NRS worksheets completed at home	
Give patient new NRS worksheets to take home	Review instructions for completion of worksheets Remind patient to bring back completed worksheets to each dialysis session
Patient worksheets	Worst Itching Intensity NRS score for the past 24 hours (complete in the dialysis unit)
Anytime During the Visit	
Record adverse events	
Anytime During Dialysis The dialysis prescription should be kept constant throughout the study, unless absolutely necessary for patient safety.	
Record procedural data	Start and stop times, net ultrafiltration, access changes, dialysis bath sodium concentration, IV iron, and ESA usage
Study Drug Administration	
Study Drug Administration	Administer an IV bolus of study drug within 15 minutes following the end of the dialysis (i.e., following return of blood to the patient)

For a subset of patients in Part A, blood samples for PK analysis will be collected from the predialyzer (arterial) line at the time points listed in the Pharmacokinetic Sampling Schedule (Appendix II, Section 18.2) (i.e., Week 8, Day 51 and 52) .

8.2.3 Weeks 9 through 12 (Part B only)

This section does not apply to the Part A of the study but only to the Part B.

8.2.3.1 Days 57, 64, 71, and 78 (Monday or Tuesday)

Days 57, 64, 71, and 78	
Anytime During the Visit prior to Study Drug Administration	
Collect and review NRS worksheets completed at home	
Give patient new NRS worksheets to take home	Review instructions for completion of worksheets Remind patient to bring back completed worksheets to each dialysis session
Patient questionnaires	Worst Itching Intensity NRS score for the past 24 hours (complete at each visit to the dialysis unit)
	Skindex-10 Scale and 5-D Itch Scale (Day 71)
	MOS Sleep Scale (Day 78)
	Patient Global Impression of Worst Itch Severity (Day 78)
Anytime During the Visit	
Record adverse events and concomitant medications	
Prior to the Start of Dialysis	
Measure vital signs (Day 57 only)	
Obtain blood for central laboratory tests (Day 57 only)	
Anytime During Dialysis The dialysis prescription should be kept constant throughout the study, unless absolutely necessary for patient safety.	
Record procedural data	Start and stop times, net ultrafiltration, access changes, dialysis bath sodium concentration, IV iron, and ESA usage
After Dialysis	
Measure body weight (Day 57 only)	
Study drug administration	Administer an IV bolus of study drug within 15 minutes following the end of the dialysis (i.e., following return of blood to the patient)

8.2.3.2 Days 59, 66, 73, and 80 (Wednesday or Thursday) and Days 61, 68, 75, and 82 (Friday or Saturday)

Days 59, 66, 73, and 80 (Wednesday or Thursday) and Days 61, 68, 75, and 82 (Friday or Saturday)	
Anytime During the Visit prior to Study Drug Administration	
Collect and review NRS worksheets completed at home	
Give patient new NRS worksheets to take home	Review instructions for completion of worksheets Remind patient to bring back completed worksheets to each dialysis session
Patient worksheets	Worst Itching Intensity NRS score for the past 24 hours (complete at each visit to the dialysis unit)
Anytime during the Visit	
Record adverse events	
Anytime During Dialysis The dialysis prescription should be kept constant throughout the study, unless absolutely necessary for patient safety.	
Record procedural data	Start and stop times, net ultrafiltration, access changes, dialysis bath sodium concentration, IV iron, and ESA usage
Study Drug Administration	
Study Drug Administration	Administer an IV bolus of study drug within 15 minutes following the end of the dialysis (i.e., following return of blood to the patient)

8.3 End-of-Treatment (Day 57 of Part A or Day 85 of Part B) or Early Termination Visit

At the End of Treatment or Early Termination Visit, which will occur on Day 57 (+3 days) for Part A, Day 85 (+3 days) for Part B, or upon early termination from the study, the following procedures/assessments will be performed.

- Collect last NRS worksheets completed at home
- Have patient complete Worst Itching Intensity NRS score in the dialysis unit
- Measure vital signs (blood pressure, heart rate, and body temperature) prior to starting dialysis
- Perform physical examination and record changes from baseline

- Obtain blood for central laboratory tests (chemistry and hematology) prior to starting dialysis
- Obtain blood for serum pregnancy test (females of childbearing potential only)
- Obtain blood for inflammatory biomarker analysis prior to starting dialysis
- Perform 12-lead ECG prior to dialysis
- Have the patient complete the last Skindex-10 Scale, MOS Sleep Scale, 5-D Itch Scale, and Patient Global Impression of Worst Itch Severity
- Have the patient complete the Patient Global Impression of Change
- Record procedural data for dialysis, including ESA and IV iron usage
- Record adverse events and concomitant medications
- Measure post-dialysis body weight and record estimated dry weight
- Record reason for early termination, if applicable.

8.4 Follow-Up Visit

The Follow-Up Visit will occur on Day 64 (+3 days) for Part A and Day 92 (+3 days) for Part B. The following procedures/assessments will be performed.

- Measure vital signs (blood pressure, heart rate, and body temperature) prior to starting dialysis
- Record adverse events and concomitant medications.

8.5 Unscheduled Visits

Unscheduled visits may be necessary for outstanding, unresolved adverse events (e.g., additional safety laboratory or clinical evaluations). At minimum, for any unscheduled visit, record the reason for the visit, any adverse events reported, and changes to concomitant medications. Additional testing (e.g., laboratory tests, vital signs, ECG, etc.) should be performed as clinically indicated. An unscheduled visit should be used to conduct unscheduled procedures during the Follow-Up Visit to follow-up clinically significant ECG or laboratory tests observed at the End-of-Treatment Visit.

9.0 Study Drug Administration

9.1 Identity of Investigational Product(s)

Please see the study Pharmacy Manual for full details.

9.1.1 Formulation of CR845 and Placebo

Study drug will be supplied by the Sponsor as a solution in 2 mL glass vials containing an extractable volume of 1.3 mL of CR845 at concentrations of 0.05 mg/mL, 0.10 mg/mL, and 0.15 mg/mL in 0.04M 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.

Matching placebo (0.04M isotonic acetate buffer, pH 4.5) will be provided in 2 mL glass vials containing an extractable volume of 1.3 mL. The composition of the placebo buffer solution is acetic acid, sodium acetate trihydrate, sodium chloride, hydrochloric acid, and water for injection. The buffer is identical to the buffer solution used in the CR845 solution and has identical appearance as the solution containing the active ingredient. The placebo buffer solution will be packaged, stored, and shipped identically to the CR845 solution.

9.1.2 Packaging, Labeling, and Storage Stability of CR845 and Placebo

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

For Part A, vials will be packaged (blinded) in boxed kits (also blinded) containing 27 vials per kit (3 extra vials for backup). For Part B, vials will be packaged (blinded) in boxed kits (also blinded) containing 40 vials per kit (4 extra vials for backup). Each patient will be assigned 1 kit upon randomization.

Labeling of the vials will include the following:

- Study protocol number
- Blinded name of study drug (CR845 or placebo IV solution)

- Temperature storage instructions (store at 25° C)
- Space for patient identification number
- Space for patient initials
- Extractable volume: 1.3 mL
- Retest date
- Name and location of Sponsor
- Kit number
- Vial number
- Administer according to study protocol
- Caution: New Drug – Limited by Federal Law (United States) to Investigational Use
- For clinical trial use only

The label on each kit will be the same as the label on an individual vial, and in addition, will provide the number of vials contained per box.

9.2 Preparation, Blinding, Administration, and Dosage of CR845 and Placebo

Study drug will be administered as an IV bolus via IV push into dialysis venous line (e.g., into the venous port) within 15 minutes following the end of dialysis (i.e., return of blood to the patient) on scheduled drug administration days (see Schedule of Events, Section 18.0). Following the bolus, the venous line will be flushed with at least 10 mL of normal saline. The patient's estimated dry weight (i.e., the target post-dialysis weight, as determined by the patient's nephrologist or dialysis unit during Screening) will be used to calculate the dose of the study drug to be administered throughout the Treatment Period.

For Part A, the study drug doses (CR845 0.5 mcg/kg, 1 mcg/kg, and 1.5 mcg/kg or placebo) will be administered as a single IV bolus 3 times a week post-dialysis for 8 weeks. For Part B, CR845 or placebo will be administered as a single IV bolus 3 times

a week post-dialysis for 12 weeks, with the dose of study drug determined based on the safety and efficacy observed in Part A.

If a patient misses a dialysis visit, the dose for that day should be withheld and dosing should resume at the next dialysis visit. The Medical Monitor should be contacted if more than 2 consecutive doses are missed. If a dose is missed, it cannot be administered on another day.

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

Information on the study drug preparation, administration, storage, supply, disposition and accountability of the study drug can be found in the Pharmacy Manual.

9.2.1 Individual Dose Labeling (CR845 and Placebo)

One syringe will be prepared for each patient.

Each syringe containing the individual dosing solution will be labeled to include the following information:

- Cara Therapeutics study number
- Blinded name of study drug ("CR845 or placebo")
- Randomization/Subject Number
- Sponsor name and location
- Date/time prepared
- Expiration date/time
- Caution: New Drug - Limited by Federal Law (United States) to Investigational Use
- Administration according to protocol
- For Clinical Trial Use Only

9.2.2 Selection of Doses Used in the Study

The combined safety and PK data from the studies CR845-CLIN1003 and CR845-CLIN2005 provided the basis for the selection of the doses and dose regimen of CR845 to be used in this study.

In the Phase 2 trial CR845-CLIN2005, the dose of 1 mcg/kg was established as an effective anti-pruritic dose in hemodialysis patients with moderate-to-severe pruritus when administered after each dialysis over a 2-week period, but the effectiveness of a dose range of CR845 was not explored. In the PK and safety studies CR845-CLIN1003 and CR845-CLIN2005 Part A, Cara Therapeutics demonstrated that CR845 was safe and well-tolerated in hemodialysis patients at dose < 2.5 mcg/kg; therefore, the objective of the present study is to assess the efficacy of 2 additional doses of 0.5 and 1.5 mcg/kg of CR845, with the goal of comparing the effectiveness and safety of 2 doses bracketing the dose shown to be efficacious in the Phase 2 trial CLIN2005 (i.e., 1 mcg/kg). These doses have been shown to be safe and well-tolerated across 2 previous trials in 70 hemodialysis patients (Studies CR845-CLIN1003 and CLIN2005) as summarized in the IB[1].

The 0.5 mcg/kg dose has been selected to determine if a dose 50% lower than the 1 mcg/kg dose provides efficacy. The intention of studying the 1.5 mcg/kg dose is to inform dosing guidance for patients who may not achieve sufficient response at the lower doses of CR845. In hemodialysis patients, somnolence appears to be sporadically reported at dose ≥ 2.5 mcg/kg; therefore, a dose of 1.5 mcg/kg was chosen, which is 50% above the effective dose determined in the Study CR845-CLIN2005.

9.3 Drug Accountability

All supplies will be maintained under adequate security by the pharmacist or approved staff at the investigator site. At the end of each injection, the used vials will be stored until the study monitor performs accountability. After accountability is performed at the end of the study, used vials and remaining unused materials (either CR845 vials or placebo vials) will be returned to the study drug distributor as per instruction to be provided by the Sponsor in the Pharmacy Manual, and certificates of destruction will be provided from the drug distributor to the Sponsor.

The site will maintain an adequate record of receipt and distribution of all trial supplies. The pharmacist (or qualified staff member), study coordinator and/or Investigator will agree not to dispense any trial medication to any person, except study patients.

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.

10.0 Prior, Concomitant, and Prohibited Medications

10.1 Prior and Concomitant Medications

Prior medications are defined as those that the patient has taken any time during the 14 days prior to the start of Screening through prior to the first dose of study drug on Day 1. The dose and type of ESAs and IV iron administered at each dialysis visit will also be recorded. 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 study (i.e., Follow-Up Visit).

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 CRF.

If currently using antihistamines (oral, IV, or topical), topical non-drug treatments (e.g., emollients, creams, oils) or oral or intravenous corticosteroids for itch, the current regimen (i.e., same drug, same dose, same route of administration, and same frequency) has been stable for 14 days prior to Screening and no change to the regimen is anticipated from Screening through the end of the Treatment Period.

If currently using opioids, gabapentin or pregabalin, the current regimen (i.e., same drug, same dose, same route of administration, and same frequency) has been stable for at least 14 days prior to Screening and no change to the regimen is anticipated from Screening through the end of the Treatment Period.

10.2 Restricted and Prohibited Medications

Restricted and prohibited medications are presented in the table below:

Drug, Drug Class, or Treatment	Restrictions Prior to Screening Period	Restrictions During Study
Investigational drug (other than the study drug)	**Not allowed** within 30 days prior to the start of Screening	**Not allowed**
Ultraviolet light-B treatments	**Not allowed** within 30 days prior to the start of Screening	**Not allowed**
Salvia divinorum and Salvinorin A	**Not allowed** within 30 days prior to the start of Screening	**Not allowed**
Naloxone, naltrexone, or mixed agonist-antagonists (e.g., buprenorphine and nalbuphine)	Allowed	**Not allowed** from the start of Screening to the end of Treatment Period
Antihistamines (oral, IV, or topical) Topical, non-drug treatments for pruritus (e.g., emollients, creams, oils)	Allowed	Allowed, but **changes to current regimen should be avoided** (i.e., same drug, same dose, same route of administration, and same frequency) from Screening to the end of Treatment Period No new medication to treat itch should be initiated.
Opioids Gabapentin, pregabalin	Not allowed if newly started within 14 days prior to Screening or if dose change anticipated from Screening through the end of Treatment Period	Allowed, but **changes to current regimen should be avoided** (i.e., same drug, same dose, same route of administration, and same frequency) from Screening to the end of Treatment Period

11.0 Assessments

11.1 Efficacy Assessments

The effect of CR845 on itch will be measured by means of the following PRO measures:

- Worst Itching Intensity NRS score
- Skindex-10 Scale
- MOS Sleep Scale
- 5-D Itch Scale
- Patient Global Impression of Change
- Patient Global Impression of Worst Itch Severity

Patients will be trained on completion of the Worst Itching Intensity NRS scale at the first Screening Visit before the Worst Itching Intensity baseline NRS measurements for eligibility are collected, and will be trained on all other PRO measures during the week prior to randomization or prior to randomization on Day 1 of the Treatment Period. All questionnaires must be completed in strict adherence to the Patient Reported Outcomes Instructions (as per Study Reference Manual).

11.1.1 Worst Itching Intensity Numerical Rating Scale

Intensity of itch will be measured using a NRS scale (Appendix III, Section 18.3) on a worksheet in which 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, both at the clinic on dialysis days and at home on non-dialysis days.

The Worst Itching Intensity NRS has been widely utilized for evaluation of chronic itch, including, uremic pruritus[2,3,6,7].

11.1.2 Patient Self-categorization of Pruritus Disease Severity

Patients will be asked to complete the Patient Self-categorization of Pruritus Disease Severity questionnaire (see Appendix IV, Section 18.4) at Screening only. Using this questionnaire, patients will select 1 of 3 patient profiles (labeled A, B or C) that most closely resembles their own profile, with profile A being the least affected by itch and

profile C being the most affected by itch. To qualify for inclusion in the study, patients must have classified themselves as having a Patient B or Patient C profile.

The Patient Self-categorization of Pruritus Disease Severity questionnaire was tested previously in a longitudinal study of uremic pruritus and found to correlate with both itch intensity as well as instruments evaluating quality-of-life[6].

11.1.3 Skindex-10 Scale

Developed specifically for uremic pruritus, the Skindex-10 Scale (Appendix V, Section 18.5) is an instrument for measurement of quality-of-life[6]. Patients are asked to fill in 1 of 7 circles numbered from 0 (labeled with the anchor phrase "never bothered") to 6 (labeled as "always bothered") for each of the 10 questions. The total score is the sum of the numeric value of each answered question. The total score is subdivided into 3 domain scores, which are sums of the scores of the following questions: disease domain (questions 1 to 3), mood/emotional distress domain (questions 4 to 6), and social functioning domain (questions 7 to 10).

The Skindex-10 Scale was found to correlate with both itch intensity as well as other instruments evaluating quality-of-life in patients with uremic pruritus[6].

11.1.4 MOS Sleep Scale

The MOS Sleep Scale (Appendix VI, Section 18.6) was developed by the Medical Outcomes Study sleep survey in order to measure sleep disturbance[8]. For most questions, the scale instructs patients to circle 1 of 6 numbers, ranging from 1 (labeled with the anchor phrase "all of the time") to 6 (labeled "none of the time"), indicating the frequency of various aspects of pruritus-related sleep disruption over the preceding week. Patients are also provided instructions to estimate the average amount of sleep per night during the past week. The 9-item Sleep Problem Index II, the 6-item Sleep Problem Index-I, and the 4-item Sleep Disturbance subscales will be calculated.

11.1.5 5-D Itch Scale

The 5-D Itch Scale was developed as a brief but multidimensional questionnaire designed to be useful as an outcome measure in clinical trials. The 5 dimensions of itch being assessed are degree, duration, direction, disability and distribution (Appendix VII,

Section 18.7). The scale has been validated in patients with chronic pruritus and has been shown to be sensitive to changes in pruritus over time[9].

11.1.6 Patient Global Impression of Worst Itch Severity

The Patient Global Impression of Worst Itch Severity is a PRO measure that assesses itch severity[10]. The scale has only 1 item, with 5 possible values ranging from none to very severe (Appendix VIII, Section 18.8).

11.1.7 Patient Global Impression of Change

The Patient Global Impression of Change is a global PRO measure that assesses the change (improvement or worsening) in overall status relative to the start of the study[11]. The scale has only 1 item, with values ranging from 1 (Very Much Improved) to 7 (Very Much Worse) (Appendix IX, Section 18.9).

11.2 Safety Assessments

The safety assessments for each patient are the following:

- Incidence and severity of adverse events
- Physical examination
- Vital signs
- 12-lead ECG
- Clinical laboratory tests

These safety assessments may be performed at time point(s) other than those listed below as described in Section 8.5, Unscheduled Visits.

11.2.1 Physical Examination

Physical examinations will include, at minimum, an examination of the heart, lungs, abdomen, extremities, neurological system, and vascular system. Clinically significant abnormalities prior to signature of 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.

11.2.2 Vital Signs

Vital signs include sitting or semi-recumbent (for at least 3 minutes) body temperature, heart rate, and blood pressure.

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. All values will then 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.

11.2.3 Electrocardiogram

The 12-lead ECGs will be obtained and read locally by the Investigator or qualified physician designee. Clinically significant abnormalities or worsening findings observed after the first dose of study drug will be reported as treatment-emergent adverse events (TEAEs).

11.2.4 Clinical Laboratory Tests

The following clinical laboratory tests will be performed and will be analyzed by 1 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 outside the ULN) and alkaline phosphatase, alanine transaminase, aspartate aminotransferase, glucose (non-fasting), blood urea nitrogen, creatinine, albumin, and electrolytes (sodium, potassium, chloride, calcium and phosphorus). Parathyroid hormone, pre-albumin, ferritin, and transferrin saturation on Day 1, 29, 43, and 57 for Part A, and Day 1, 29, 43, 57, and 85 for Part B.
Serum pregnancy:	Women of childbearing potential only

Follicle stimulating hormone:	Women who have been amenorrheic for at least 1 year and are between 45 and 55 years of age to confirm that they are not of childbearing potential

11.3 Adverse Events

11.3.1 Definition of Adverse Events

The period of adverse event reporting will start after the signing of the ICF through the study follow-up visit or early termination visit (or 7 days after the last dose if no early termination visit was conducted).

All adverse events that occur during this reporting period will be collected for all patients, including patients who are deemed to be a screen failure (i.e., patient did not meet the eligibility criteria) and will not be randomized into the study after signing of the ICF. Adverse events will be classified as TEAE or non-TEAE based on the time of occurrence in relation to the first dose of study drug.

A TEAE can be any unfavorable and unintended sign (e.g., including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study drug, whether or not it is considered to be study drug related. A TEAE also includes any worsening (i.e., any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug. A pre-existing condition is a condition that is present prior to signing an ICF, which has been recorded as medical history. A worsening of a pre-existing condition should be captured as an adverse event if the frequency, intensity, or character of the condition worsens after the use of study drug as judged by the Investigator (i.e., to a clinically significant extent).

Treatment-emergent adverse events will be therefore defined as those events which

- Start any time after the first dose of study drug up to the follow-up visit or early termination visit (or 7 days after the last dose if no early termination visit was conducted), whichever is later.
- Increase in frequency or severity any time after the first dose of study drug up to the follow-up visit or early termination visit (or 7 days after the last dose if no early termination visit was conducted), whichever is later.

Clinically significant abnormalities prior to signing the ICF will be reported as medical history, unless they are expected findings from medical history that have already been reported. Any new or significantly worsened clinically significant abnormalities occurring after the patient signs informed consent should be entered as adverse events.

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

Following signature of the ICF, any adverse event that results in hospitalization or prolonged hospitalization should be reported as an SAE as described below.

Overdose is defined as an accidental or intentional exposure to study drug at a dose higher than specified in the protocol or higher than known therapeutic dose. An overdose of study drug must be reported as a major protocol deviation. If the overdose is associated with clinical signs or symptoms, then these should be captured as adverse events.

11.3.2 Adverse Event Intensity Assessment

The Investigator will assess the intensity of each adverse event reported during the study. The assessment will be based on the Investigator's clinical judgment. The intensity of each adverse event should be assigned to 1 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

11.3.3 Definition of Serious Adverse Events

An SAE is any adverse event occurring at any dose and regardless of causality that:

- Results in death
- Is life-threatening. Life-threatening means that the patient was at immediate risk of death from the reaction as it occurred (i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form). For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.
- Requires in-patient hospitalization (hospital admission, not an emergency room visit) or prolongation of existing hospitalization. Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry (i.e., prior to signing of the informed consent) are not considered adverse events if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected manner during the study (e.g., surgery performed earlier than planned). For example, for patients on the transplant waiting list prior to study entry, a renal transplant would not be considered an SAE. If complications occur as a result of transplant surgery, these complications will need to be evaluated for SAE criteria.
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a patients' ability to conduct normal life functions
- Is a congenital anomaly/birth defect
- Is an important medical event. An important medical event is an event that may not result in death, be life threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs.

Severe versus serious adverse events: An adverse event that is assessed as severe should not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both adverse events and SAEs can be assessed as severe. The term "severe" is

often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based 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.

11.3.4 Adverse Event Causality or Relatedness to the Study Drug

Every effort should be made by the Investigator to try to explain each adverse event and assess its relationship, if any, to the study drug. The temporal relationship of the event to study drug administration should be considered in the causality assessment (i.e., if the event starts soon after study drug administration and resolves when the study drug is stopped). The Investigator should not assume that any adverse event is necessarily drug-related, but should complete a thorough and diligent medical workup to investigate any other possible medical causes of the adverse event.

Adverse events will be classified by the Investigator as follows:

Definitely Related

There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The event resolves or improves upon withdrawal of drug (dechallenge). The event would be considered as definitely related to the study drug upon results of a positive rechallenge procedure.

Probably Related

There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time sequence to administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge), if dechallenge was done.

Possibly Related

There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g., the patient's clinical condition, other concurrent disease, concomitant medications or events). Although an adverse drug reaction may be classified only as "possible" soon after discovery, it can be flagged as requiring more information, and later be upgraded to "probably related" or "definitely related", if appropriate.

Unlikely Related

A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or concurrent or underlying disease provide plausible explanations (e.g., the patient's clinical condition, other concomitant treatments).

Not related

The adverse event is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

11.3.5 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 CRF from the time the patient signs the ICF and until the Follow-Up Visit/early termination (or 7 days after the last dose if no early termination visit was conducted), whichever is later, 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 associated with the use of study drug.

Each adverse event is to be documented with verbatim term, start and stop date and time, intensity, causal relationship with the 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.

All SAEs will be documented on the SAE form.

The reporting period for all adverse events begins with the signature of the ICF and ends at the study Follow-Up Visit or 7 days following the last dose of study drug, whichever is later. All AEs should be followed until they resolve or the Investigator assesses them as stable or the subject's participation in the trial ends, whichever comes first. . In addition, all assessed by the Investigator as definitely or possibly or probably related to the study medication that are ongoing at the time of the patient's last visit, should continue to be followed even after the subject's participation in the trial is over. Such events should be followed until they resolve or until the Investigator assesses them as "stable." Resolution of such events is to be documented on the appropriate CRF.

SAEs that occur after the Follow-Up Visit and up to 30 days thereafter should also be documented on an SAE form if they are deemed by the Investigator to be "definitely related", "probably related", or "possibly related" to the study drug. SAEs that occur after the Follow-up Visit and up to 30 days thereafter do not need to be documented on an SAE form if they are deemed by the Investigator to be "unlikely related" or "not related" to study drug.

11.3.6 Serious Adverse Event Notification, Documentation, and Reporting

The Investigator will immediately notify the Medical Monitor/Sponsor by telephone of any patient deaths or life-threatening events, whether related or unrelated to the study drug.

The Investigator will notify the Medical Monitor/Sponsor within 24 hours regarding any SAEs other than death and immediately life-threatening events, regardless of relationship to study drug.

The Investigator will also complete an SAE Report form (according to SAE and Pregnancy Report Form Completion Guidance) and will email or fax it within 24 hoursto Biorasi Drug Safety and Pharmacovigilance for case processing as defined in the Safety Management Plan:

E-mail: safety@biorasi.com

Fax: +1 (786) 221-3531

SAE report form will be completed regardless of relationship to the study drug.

In the event of any SAE (other than death) occurring after the last treatment day 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 Investigator will not delay reporting anSAE (following the directions above) 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.

The Medical Monitor or designee may contact Biorasi Drug Safety and Pharmacovigilance for further information or clarification on the reported SAE. Biorasi Drug Safety and Pharmacovigilance will then contact the Investigator to obtain further information or clarification, or any other requested supporting documentation and will forward any information received to the Medical Monitor. In some instances, the Medical Monitor may contact the PI directly for further information.

The name and contact information for the Medical Monitor is:

Sarbani Bhaduri, MD
Telephone: (415) 613-6514
Email: sbhaduri@caratherapeutics.com

Alternate contact will be provided in the Safety Management Plan.

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 Institutional Review Board (IRB).

It is the responsibility of Cara Therapeutics to send all regulatory reports to the FDA. Adverse events that are serious and related to the study drug and unexpected will be reported to the regulatory authorities 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 purposes, Cara Therapeutics can upgrade the Investigator's assessment (e.g., from not related to related); however, Cara Therapeutics cannot downgrade the Investigator's assessment unless the Investigator determines that a re-assessment of causality is necessary. The Medical Monitor will review and comment on any upgrade made to a report. If there is any doubt concerning the relationship between the drug and the event, then the relationship should be considered drug related.

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

Further details about SAE reporting and processing will be provided in a Safety Management Plan.

11.4 Pharmacokinetic Evaluation

For PK analysis, in the subset of patients who consented to participate in the PK analysis, blood samples will be collected from the predialyzer (arterial) line at the time points listed in the Pharmacokinetic Sampling Schedule (Appendix II, Section 18.2). The actual time of collection will be recorded. Plasma samples will be analyzed for CR845 using liquid chromatography with tandem mass spectrometric detection according to validated analytical methods. Full details of the methodology and results for bioanalytical and PK analysis will be presented in separate reports, which will be appended to the clinical study report.

Detailed instructions for PK sample collection and processing will be provided in the lab manual.

11.5 Inflammatory Biomarker Evaluation

Inflammatory biomarkers will include hepcidin, IL-2, IL-6, IL-31, and C-reactive protein. Additional biomarkers of interest may be evaluated and will be identified in the Statistical Analysis Plan and laboratory manual, as applicable. A blood sample of sufficient volume to provide for replicate assays of each biomarker, as specified by the laboratory performing the analysis, will be collected prior to dialysis on Day 1 and at the end of the Treatment Period. If the patient misses the last visit of the Treatment Period,

the sample may be collected at their next dialysis visit for the same week. The actual time of sample collection will be recorded.

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

12.0 Statistical Methods

12.1 General Considerations

A statistical analysis plan (SAP) will be developed based on the latest version of the clinical protocol and CRFs and finalized prior to unblinding of the study. 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 for the data summary and analysis of safety and efficacy variables. This protocol describes key analyses as currently contemplated. 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 non-missing observations, mean, standard deviation, median, minimum, and maximum; categorical variables will be summarized using the frequency count and the percentage of patients in each category. In addition to the descriptive summaries, pertinent data listings will be provided to facilitate case studies.

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

12.2 Determination of Sample Size

Part A: Approximately 160 male and female hemodialysis patients with moderate-to-severe pruritus will be randomized at approximately 40 clinical sites. A subset of up to 40 patients (approximately 10 per treatment group) will be consented for the collection of blood samples for evaluating the PK profile of CR845. No formal sample size calculation was performed to select this sample size. However, a sample size of 40 patients per group is adequate to provide an appropriate estimate of the magnitude and variability of treatment effect at each dose, and select the appropriate dose to be further evaluated compared to placebo in Part B.

Part B: Approximately 240 male and female hemodialysis patients with moderate-to-severe pruritus will be randomized at approximately 60 clinical sites.

[redacted]

[redacted]

12.3 Interim Analysis

No formal interim analysis of efficacy data is planned.

An ongoing review of the cumulative safety data for this study will be conducted by an external DMC for both Part A and Part B of this study. The operation of the DMC will be governed by a charter that will describe the groups' frequency of meeting, procedures (including, but not limited to, periodic safety monitoring) and requirements for reporting its observations to the Sponsor.

12.4 Analysis Populations

The Safety and Full Analysis Populations are both defined as the group of all randomized patients who received at least 1 dose of double-blind study drug. Following the intent-to-treat principle, patients in the Full Analysis Population will be analyzed according to their randomized treatment, regardless of the actual treatment received. However, patients in the Safety Population will be analyzed according to their actual treatment. The Safety Population will be used to analyze all safety endpoints while the Full Analysis Population will be used to analyze all efficacy endpoints.

The Per-Protocol Population is defined as the subset of patients in the Full Analysis Population who do not have any major protocol deviations that could affect the efficacy analyses. An analysis of the primary and secondary efficacy variables for the Per-Protocol Population may be performed if more than 20% of the patients in the Full Analysis Population are excluded.

Membership in the Per-Protocol Population will be determined prior to unblinding the data and will be detailed in the SAP.

The Pharmacokinetic Evaluable Population is defined as all patients who received CR845 and had sufficient plasma concentrations for PK analysis.

12.5 Statistical Summary and Analysis

12.5.1 Patient Disposition

The number of patients randomized, completed, or discontinued from the study, along with the reason for discontinuation, will be presented overall and by treatment group. Patient count by analysis population will also be tabulated.

12.5.2 Protocol Deviations

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

12.5.3 Demographic and Baseline Characteristics

Demographic and other baseline characteristics will be summarized by treatment group.

12.6 Efficacy Analysis

12.6.1 Primary Efficacy Endpoint

The primary efficacy endpoint is defined as the change from baseline to the last week of the Treatment Period (Week 8 for Part A, and Week 12 for Part B) with respect to the weekly mean of the daily 24-hour Worst Itching Intensity NRS score. The weekly mean of the 24-hour Worst Itching Intensity NRS score will be defined as the sum of the daily Worst Itching Intensity NRS score reported during a specific week (Days 2-8; Days 9-15; Days 16–22; etc.) divided by the number of days with non-missing scores for that week. If the daily worst itching score is missing for > 3 days during a specific week, the corresponding weekly mean worst itching score will be set to missing. The baseline score will be defined as the average of the daily worst itching scores over the last 7 days prior to randomization, including pre-treatment assessments collected on Day 1.

The primary efficacy variable will be analyzed using a mixed effects model with repeated measures (MMRM). The model will contain treatment, week, and treatment-by-week interaction as fixed effects; baseline as a covariate, and patient as a random effect. The baseline score will be defined as the mean of the 24-hour worst itching score over the last

7 days prior to randomization, including pre-treatment assessments collected on Day 1. For each dose group (Part A) or for the selected dose of CR845 (Part B), the treatment group difference versus placebo will be estimated as the simple contrast in the treatment effect on the last week of treatment.

An appropriate covariance matrix will be used to model the within-patient errors. The use of an unstructured covariance matrix structure as well as other structures, such as spatial patterns, that require fewer parameters (Toeplitz, autoregressive autoregressive [1], or compound symmetry) will be examined. The Akaike information criterion will be used to determine the appropriate covariance matrix for the MMRM model. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom.

In the primary efficacy analysis (both Part A and Part B), missing daily worst itching scores will not be imputed. Assuming that the data are missing at random (MAR), the estimates of the treatment differences calculated from the MMRM model described above are unbiased.

Sensitivity analyses will be conducted to evaluate the effect of the MAR assumption on the study results for Part B as described below. Depending on the pattern and the amount of early treatment discontinuations in Part A, similar sensitivity analyses may also be performed for Part A in order to provide estimates of treatment effect under different imputation algorithms and help refine the sample size for Part B.

Sensitivity analysis 1 (Multiple Imputation; MAR):

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

- Intermittent missing data will first be imputed using the Markov Chain Monte Carlo (MCMC) method implemented with the SAS MI procedure, which is appropriate for non-monotonic missing data.
- Data missing after patients discontinue treatment early will then be multiply imputed with the SAS MI procedure using a method appropriate for monotone missingness (e.g., regression statement).

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

Sensitivity analysis 2 (Multiple Imputation; Missing Not at Random):

This sensitivity analysis is an implementation of a pattern mixture model that uses control data for pattern imputation[12]. The authors also provide appropriate SAS code. It assumes that patients who discontinue early in any of the 3 active treatment groups will have the same evolution, after treatment is stopped, as patients in the placebo group (who are not exposed to active treatment, by definition). Patients who discontinue treatment early in the placebo group are assumed to behave as the placebo patients that remain in the study.

- Intermittent missing data will first be imputed using the MCMC method implemented with the SAS MI procedure, which is appropriate for non-monotonic missing data.

- Data missing after patients discontinue treatment early will be multiply imputed using multiple calls of the SAS MI procedure. At each time point, missing data will be imputed using data from patients in the placebo group that have complete data at that time.

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

Sensitivity Analysis 3 (Single Imputation; Hybrid Baseline Observation Carried Forward/Last Observation Carried Forward):

- Intermittent missing data will not be imputed.

- For patients who discontinued study drug due to adverse events, data missing after discontinuation will be imputed using the baseline value of the daily worst itching score.

- For patients who discontinue due to reasons other than adverse event, missing data will be imputed using the last observation carried forward.

12.6.2 Secondary Efficacy Endpoint

The secondary efficacy variable is the change from baseline in the (total) Skindex-10 Scale score. An MMRM, similar to that used for the primary efficacy analysis, will be fitted to the data. The baseline value will be defined as the value of the Skindex-10 Scale score collected on Day 1, prior to randomization. For each dose group, the treatment group difference versus placebo will be estimated as the simple contrast in the treatment effect at Week 8 (Part A) or Week 12 (Part B).

Missing Skindex-10 Scale scores will not be imputed. Assuming that the data are MAR, the estimates of the treatment differences calculated from the MMRM models above are unbiased.

12.6.3 Hypothesis Testing Strategy

PART A

The primary goal for Part A of this clinical investigation is to evaluate the efficacy of different dose levels of IV CR845 administered after each dialysis session in reducing the intensity of itch over an 8-week Treatment Period in hemodialysis patients with moderate-to-severe pruritus. Three doses will be studied (1.5 mcg/kg, 1.0 mcg/kg, and 0.5 mcg/kg), and each will be compared against placebo. One of these doses will be selected for further evaluation compared to placebo in Part B. Although a hypothesis test of each CR845 dose against placebo will be performed for each of the primary, secondary and exploratory variables, these hypothesis tests are not expected to be statistically significant based on the planned sample size of approximately 40 patients per treatment group and effect size data from previous studies of CR845 in the same population. Nevertheless, the estimates of treatment effect and p-values resulting from these hypothesis tests will be used, in addition to a review of safety data, to select the most appropriate dose for Part B. A sample size of 40 patients per group is adequate to provide an appropriate estimate of the magnitude and variability of treatment effect at each dose.

PART B

Each hypothesis test will be 2-sided and conducted at the 5% significance level. The study will be considered positive if the null hypothesis of no treatment difference is rejected in favor of the alternative that patients randomized to CR845 experience

significantly less itching as measured by the change from baseline to Week 12 of the Treatment Period with respect to the weekly mean of the 24-hour Worst Itching Intensity NRS score.

12.6.4 Other Efficacy Endpoints

12.6.4.1 Itch Intensity Measures

- Change from baseline with respect to the weekly mean of the 24-hour Worst Itching Intensity NRS score from Week 2 through the end of the Treatment Period (Week 8 for Part A or Week 12 for Part B). Treatment differences with respect to this variable will be evaluated using the same MMRM model fitted for the primary efficacy analysis.

- Treatment Response defined as the percent improvement from baseline with respect to the weekly mean of the 24-hour Worst Itching Intensity NRS score during the last week of the Treatment Period (Week 8 for Part A or Week 12 for Part B):

  If a patient's mean daily itch score during the last week of the Treatment Period is greater than their baseline score (i.e., the patient has an increase in itch compared to baseline), his/her response to treatment will be assigned a value of 0. The treatment response for patients who discontinue treatment early will be estimated depending on the reason for discontinuation. For patients who discontinue due to their underlying condition (i.e., non-treatment related adverse event), the treatment response will be estimated by carrying forward the last non-missing weekly mean worst itch score. Patients who discontinue due to any other reason will be considered non-responders and will be assigned a treatment response value of 0.

  A graph of percentage of patients who have a treatment response ≥ 10%, ≥ 20%, ≥ 30%, ≥ 40%, ≥ 50%, ≥ 60%, ≥ 70%, ≥ 80%, ≥ 90%, and ≥ 100% will be presented. In addition, the proportion of patients with a response to treatment that is ≥ 20% will be analyzed using logistic regression, including treatment and baseline itch score as independent variables. The cutoff of 20% was shown to be clinically significant in a longitudinal study of uremic pruritus in hemodialysis patients[6]. This analysis may be repeated for other cutoffs.

12.6.4.2 Itch-Related Quality-of-Life Measures

- Change from baseline in itch-related quality-of-life from Week 2 through the last week of the Treatment Period (Week 8 for Part A or Week 12 for Part B) as assessed by the total Skindex-10 Scale scores. Treatment differences will be evaluated using the same MMRM model fitted for the analysis of the change from baseline in the overall Skindex-10 Scale score (secondary efficacy endpoint).

- Change from baseline in itch-related quality-of-life at the end of the last week of the Treatment Period (Week 8 for Part A or Week 12 for Part B), and over each week of the Treatment Period within each of the 3 domains of the Skindex-10 Scale. Treatment differences with respect to each domain will be evaluated using the same MMRM model fitted for the analysis of the change from baseline in the overall Skindex-10 Scale score (secondary efficacy endpoint).

- Change from baseline to the end of Week 8 (Part A) or Week 12 (Part B) in itch related quality-of-life, as measured by the 5-D Itch Scale. An MMRM, similar to the one used for the primary efficacy analysis, will be fitted to the data. In Part A, the model will contain treatment (4 levels: 0.5 mcg/kg; 1.0 mcg/kg; 1.5 mcg/kg or placebo), week, and treatment by week interaction as fixed effects; baseline as a covariate; and patient as a random effect. The baseline value will be defined as the value of the 5-D Itch Scale score collected on Day 1, prior to randomization. In Part B, the model will be similar except that there will only be 2 levels for treatment (CR845 and placebo). For each dose group, the treatment group difference versus placebo will be estimated as the simple contrast in the treatment effect at Week 8 (Part A) or Week 12 (Part B).

- Change from baseline to the end of Week 8 (Part A) or Week 12 (Part B) in itch related sleep disturbance, as measured by the Sleep Disturbance Subscale of the MOS Sleep Scale. An MMRM, similar to the one used for the primary efficacy analysis, will be fitted to the data. In Part A, the model will contain treatment (4 levels: 0.5 mcg/kg; 1.0 mcg/kg; 1.5 mcg/kg or placebo), week, and treatment by week interaction as fixed effects; baseline as a covariate; and patient as a random effect. The baseline value will be defined as the value of the Sleep Disturbance Subscale score collected on Day 1, prior to randomization. In Part B, the model will be similar except that there will only be 2 levels for treatment

(CR845 and placebo). For each pairwise comparison against placebo, the treatment group difference will be estimated as the simple contrast at Week 8 (Part A) or Week 12 (Part B).

- Proportion of patients who rate their itch condition as "Very Much Improved" or "Much Improved", as measured by the Patient Global Impression of Change at the end of the Treatment Period (Week 8 for Part A or Week 12 for Part B): Pairwise treatment differences with respect to this variable will be tested using the Fisher's exact test.

- The number and percentage of patients in each of the 5 categories of the Patient Global Impression of Worst Itch Severity at baseline, Weeks 2, 4, and 8 (Part A), or baseline, Weeks 2, 4, 8, and 12 (Part B), will be tabulated. In addition, the proportion of patients who have a 1-point improvement or more at Week 2, 4, 8, and Week 12 (Part B only), as measured by the Patient Global Impression of Worst Itch Severity. Pairwise treatment differences with respect to this variable will be tested using the Fisher's exact test.

12.6.4.3 Missed Dialysis Visits and Incidence of Infection

- Missed dialysis visits based on percentage of patients who missed 1 or more visits at the dialysis unit and total number of missed dialysis visits during the Treatment Period. Statistical analyses will be defined in the SAP.

- Incidence of infections based on adverse events, hospitalizations, and/or use of antibiotics for treatment of infection related to uremic pruritus. The rate of infections will be analyzed using logistic regression. Baseline factors known to be correlated to the risk of infection in hemodialysis patients may be included in the analysis.

12.6.4.4 Inflammatory Biomarkers, ESA, and IV Iron Use

- Changes in inflammatory biomarkers (e.g., hepcidin, IL-2, IL-6, IL-31, C-reactive protein) from pre-dose to the end of the Treatment Period. Statistical analyses will be defined in the SAP.

- Changes in ESAs, IV iron dose, and erythropoiesis resistive index from pre-dose to the end of the Treatment Period. Statistical analyses will be defined in the SAP.

12.6.5 Additional Statistical Considerations

Part A:

For each analysis variable (primary, secondary, exploratory), all pairwise comparisons against placebo will be evaluated. Pairwise comparisons between each dose will be conducted but will be considered secondary. There will be no adjustments for multiplicity.

A dose-response analysis of the primary and secondary variable will also be conducted. In this case, the null hypothesis of no dose response will be tested against the 1-sided alternative that the treatment effect increases linearly with dose. A dose-response analysis of the exploratory variables may be considered. Further details will be included in the SAP.

In addition, an analysis of all CR845 doses combined against placebo will be performed with respect to the primary and secondary variables. An analysis of all CR845 doses combined versus placebo with respect to the exploratory variables may be considered. Further details will be included in the SAP.

Part B:

In Part B, only 1 dose will be evaluated against placebo. As defined in the previous section, Part B will be considered positive if the primary efficacy analysis rejects the null hypothesis of no treatment difference. There will be no adjustment for multiplicity for the secondary variables.

12.7 Pharmacokinetic Analysis

Plasma concentrations will be summarized descriptively and graphically by nominal time. Pharmacokinetic parameters (C_{max}, time to C_{max}, AUC, clearance, steady state volume of distribution, and accumulation factors) will be calculated based on the actual time of blood sampling, listed and summarized. Accumulation ratios for C_{max} (R_{Cmax}) and AUC (R_{AUC}) will also be calculated. Individual plasma CR845 concentrations will be listed

and plotted by patient. Details of the PK analyses and PK tables, listings and figures will be provided in a separate PK analysis plan.

12.8 Safety Analysis

Analysis of all safety data will be performed on the Safety Population and will be summarized by the treatment received. The SAP will detail the analyses that will be applied to each safety parameter.

The objective of the evaluation of the safety variables is to investigate the data for any effects on clinical tolerability, vital signs, ECG, and laboratory tests. All safety variables will be summarized by treatment group (and time point as appropriate). The general strategy of the safety analysis will be to examine the data summaries for any differences from placebo and any trends among the dose levels. No formal hypothesis testing will be carried out and no formal statistical analysis of the safety parameters will be performed.

Summaries of the data for use of prior and concomitant medications; vital signs; 12-lead ECGs; clinical safety laboratory evaluations; adverse events (including SAEs); and other relevant safety parameters will be presented in addition to by-patient listings of all safety data.

12.8.1 Adverse Events

All adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA). The MedDRA treatment dictionary will be used to map adverse events verbatim to system organ class (SOC) and MedDRA preferred term for standardization and summary purposes.

All reported adverse events (regardless of treatment-emergent or not) will be included in a by-subject adverse event listing. Only TEAEs will be included in summary tables. TEAES will be defined as any AEs occurring starting after the first dosing of the study drug. The number and percentage of patients experiencing TEAEs will be summarized for each treatment group. The incidence of TEAEs will be presented by the counts and percentages of patients with adverse events. A patient will be counted only once in the incidence count for a MedDRA preferred term, although a patient may have multiple occurrences (start and stop) of an event associated with a specific MedDRA preferred term. The most frequent TEAEs (greater than 5% per group) will also be tabulated for each treatment group by SOC and preferred term.

The incidence and percentage of patients experiencing treatment-emergent SAEs and TEAEs leading to study discontinuation will be presented for each treatment group by appropriate MedDRA SOC and preferred term.

Tabulations of TEAEs will include summaries by:

- by SOC, preferred term, and severity and
- by SOC, preferred term, and relationship to study drug (not related versus related).

Treatment-emergent adverse events considered by the Investigator to be "definitely related," "probably related," or "possibly related" to the study drug will be characterized as "related" to the study drug. Treatment-emergent adverse events considered by the Investigator to be "unlikely related" or "not related" to the study drug based on the definitions below will be characterized as "not related" to the study drug.

If the severity and/or relationship to the study drug of an adverse event is missing, a worst-case scenario will be assumed (i.e., the adverse event will be defined as "severe" and/or "definitely related" to the study drug).

Deaths, non-fatal SAEs, and adverse events leading to treatment discontinuation or dose interruption will be listed including the treatment group, start and stop dates of the adverse event, and days on study relative to the start of adverse event (if applicable).

No statistical tests will be performed on adverse event data.

12.8.2 Other Safety Analyses

Summary statistics for each scheduled time point measured and mean changes from baseline to each time point (when applicable) will be presented. This will apply to the assessment of vital signs and clinical safety laboratory evaluation. Clinically significant new or worsening findings on physical examinations and ECGs will be collected as adverse events. The baseline value will be defined as the last value obtained prior to the first dose of study drug and includes both scheduled and repeat (unscheduled) observations.

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. Within treatment comparisons will be based on 3 by 3 tables (shift tables) that, for a particular laboratory test, compare the baseline LNH classification to the LNH classification at the end of double-blind treatment.

12.8.3 Prior and Concomitant Medications

Medications will be coded using the World Health Organization Drug Dictionary.

All prior medications will be summarized by treatment group using the Anatomical-Therapeutic-Chemical code and preferred term. Similar summaries will be produced for all concomitant medications. In addition, a summary of all prior and concomitant medications used to treat the patient's chronic pruritus may be produced.

13.0 Quality Control and Quality Assurance

13.1 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 CRFs 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 by personal visits from a representative of the Sponsor or its designee (site monitor) who will review patient enrollment, CRFs, 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 trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements. Monitoring reports will be submitted to the Sponsor in a timely fashion as per details described in a clinical monitoring plan for this study.

13.2 Audits and Inspections

The investigational site will maintain appropriate medical and research records for this trial, in compliance with International Conference on Harmonisation (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 trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic

negatives, microfilm or magnetic media, x-rays, and participant files and records kept at the pharmacy, laboratories, or medical-technical departments involved in the clinical trial, as applicable.

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

13.3 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.

14.0 Ethics and Regulatory Compliance

14.1 Ethics

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki (Edinburgh 2000) 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.

A properly constituted, valid IRB or Independent Ethics Committee (IEC) must review and approve the protocol, the Investigator's informed consent document, and related patient information and recruitment materials 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. No amendments to the study protocol should be made without the prior written agreement of the Investigator, the Sponsor, and the IRB.

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

14.2 Good Clinical Practices

The study will be conducted in accordance with the ICH for GCP and the appropriate regulatory requirement(s). The Investigator will be thoroughly familiar with the

appropriate use of the study drug as described in the protocol, 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 trial master file will be established at the beginning of the study, maintained for the duration of the study, and retained according to the appropriate regulations.

14.3 Institutional Review Board

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

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

14.4 Informed Consent Process

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and which continues throughout the individual's study participation. The Investigator or designee will discuss extensively with the participant patient the study risks. Copies of the 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. Consent forms will be IRB approved and the participant will be asked to read and review the document. Upon reviewing the document, the Investigator or designee will explain the research study to the participant and answer any questions that may arise. The participants will sign the ICF prior to any procedures being done specifically for the study. The participants should have sufficient opportunity to discuss the study and process the information in the consent process prior to agreeing to participate. The participants may withdraw consent at any time throughout the course of the study. A signed copy of the ICF will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study or withdraw during the course of the study.

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 guidelines. Prior to the beginning of the trial, the Investigator must have written approval/favorable opinion from the IRB of the written ICFs and any other written information to be provided to the participants. It is the responsibility of the Investigator to ensure that written informed consent is obtained from the patient before any activity or procedure is undertaken that is not part of routine care.

14.5 Patient Confidentiality

In order to maintain patient privacy, all CRFs, study drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor, or its designee, and regulatory authority access to the patient's original medical records for verification of data gathered on the CRFs 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.

14.6 Study Suspension, Termination and Completion

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 IRBs/IECs are notified as appropriate.

Should the study be closed prematurely, all study materials (completed, partially completed, and blank CRFs, study drug, etc.) must be returned to Cara Therapeutics or destroyed at the site if authorized by Cara Therapeutics.

15.0 Data Handling and Record Keeping

15.1 Case Report Form Completion

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

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

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

15.2 Data Management Responsibilities

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

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

16.0 Administrative Procedures

16.1 Study Records Retention

The Investigator will retain all study records according to ICH-GCP and applicable regulatory requirement(s) (generally 2 years after discontinuing clinical development or after the marketing approval of the study drug). The Investigator agrees to adhere to the document retention procedures by signing the study protocol. Records will be retained until notified by Cara Therapeutics in writing that the records may be destroyed. The Investigator shall take responsibility for maintaining adequate and accurate hard copy source documents of all observations and data generated during this study, including any data clarification forms received from the Sponsor. Such documentation is subject to inspection by Cara Therapeutics, its representatives, and regulatory authorities. If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. If a custodial change or a change in record location occurs, Cara Therapeutics must be notified in writing.

16.2 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. Major protocol deviations will be summarized in the final clinical study report and all protocol deviations will be presented in a listing.

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

16.3 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 is 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.

17.0 References

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18.0 Appendices

18.1 APPENDIX I Schedule of Events

PART A									
Study Procedures	**Screen**	**Treatment Period[a]**						**End of Treatment/ Early Termination**	**Follow-Up**
	Day -14 to Day -1	**Week 1**			**Week 2 to 8**				**+7 days after EOT**
		M/Tu	**W/Th**	**F/Sa**	**M/Tu**	**W/Th**	**F/Sa**		
Visit Days →	**-14 to -1**	**1**	**3**	**5**	**8**	**10**	**12**	**57 (+3)**	**64 (+3)**
					15	**17**	**19**		
					22	**24**	**26**		
					29	**31**	**33**		
					36	**38**	**40**		
					43	**45**	**47**		
					50	**52**	**54**		
Administrative Procedures									
Informed Consent	X								
Inclusion/Exclusion Criteria	X	X[b]							
Medical History	X	X[b]							
Randomization		X							
Safety and Efficacy Evaluations									
Physical Examination	X							X	
Height	X								
Weight (estimated dry body weight)	X	X						X	
Post-dialysis weight		X						X	
12-lead Electrocardiogram	X[c]	X[c]			X[c]			X[c]	
Pre-dialysis Vital Signs[d]	X	X			X[e]			X	X
Hematology, Serum Chemistry (pre-dialysis)	X	X[f]			X[f]			X[f]	
Serum Pregnancy (females of childbearing potential only)	X							X	
FSH	X[g]								

PART A - Continued									
Study Procedures	**Screen**	**Treatment Period[a]**						**End of Treatment/ Early Termination**	**Follow-Up**
	Day -14 to Day -1	**Week 1**			**Week 2 to 8**				**+7 days after EOT**
		M/Tu	**W/Th**	**F/Sa**	**M/Tu**	**W/Th**	**F/Sa**		
Visit Days →	**-14 to -1**	**1**	**3**	**5**	**8**	**10**	**12**	**57 (+3)**	**64 (+3)**
					15	**17**	**19**		
					22	**24**	**26**		
					29	**31**	**33**		
					36	**38**	**40**		
					43	**45**	**47**		
					50	**52**	**54**		
Safety and Efficacy Evaluations									
Patient Self-categorization of Pruritus Disease Severity	X								
Patient training on PRO Worksheets	X[h,i]	X							
Worst Itching Intensity NRS (daily)	X	X						X	
Skindex-10 Scale, MOS Sleep Scale, 5-D Itch Scale, Patient Global Impression of Worst Itch Severity		X[j]			X[j,k]			X	
Patient Global Impression of Change								X	
Record procedural data for dialysis (including ESA and IV iron)	X	X	X	X	X	X	X	X	
IV administration of study drug after dialysis		X	X	X	X	X	X		
Inflammatory biomarker samples[l]		X						X	
Adverse Event Monitoring	X	X						X	X
Prior Medications	X								
Concomitant Medications		X[m]			X[m]			X	X

EOT=end of treatment; ESA= erythropoiesis-stimulating agent; F=Friday; FSH=follicle-stimulating hormone; IV=intravenous; M=Monday; MOS=Medical Outcomes Study; NRS=numerical rating scale; PRO=patient reported outcome; Sa=Saturday; Th=Thursday; Tu=Tuesday; W=Wednesday;

See footnotes as well as Section 8 and 11 for additional procedural details.

[a] Each visit during the Treatment Period will coincide with the patient's normal dialysis treatments.

[b] Medical history will be updated on Day 1 with any changes since the Screening Visit, and inclusion/exclusion criteria will be confirmed prior to randomization.

[c] Electrocardiogram must be performed prior to dialysis at Screening, Day 1, Day 29, and Day 57 (or early termination).

[d] Vital signs will be obtained in a sitting or semi-recumbent position (for at least 3 min) and will include body temperature, heart rate, and blood pressure.

[e] On Day 15 and 29 only, pre-dialysis vital signs should be recorded

[f] On Day 1, 15, 29, 43, and 57 only. Serum chemistry should include parathyroid hormone, pre-albumin, ferritin and transferrin saturation.

[g] Obtain on women who have been amenorrheic for at least 1 year and are between 45 and 55 years of age.

[h] Training on Worst Itching Intensity NRS only

[i] Training on Skindex-10 Scale, MOS Sleep Scale, 5-D Itch Scale and Patient Global Impression of Worst Itch Severity scales may be performed at any time during the week prior to randomization.

[j] To be performed prior to or during dialysis, but must be completed prior to dosing.

[k] Skindex-10 Scale and 5-D Itch Scale completed on the first visit of Week 3, 5, and 7 (Day 15, 29, and 43, respectively). MOS Sleep Scale completed on the first visit of Week 4 and 8 (Day 22 and 50, respectively). Patient Global Impression of Worst Itch Severity completed on the first visit of Week 2, 4, and 8 (Day 8, 22, and 50, respectively). If the first visit of the week is missed, the patient may complete the procedures at their next visit for the same week. Questionnaires will be completed in strict adherence to the Patient Reported Outcomes Instructions (as per Study Reference Manual).

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

[m] Concomitant medications will be updated on a weekly basis at the beginning of each week. Prior medications will be recorded until the time of first dosing.

PART B									
Study Procedures	**Screen**	**Treatment Period[a]**						**End of Treatment/ Early Termination**	**Follow-Up**
	Day -14 to Day -1	**Week 1**			**Week 2 to 12**				**+7 days after EOT**
		M/Tu	**W/Th**	**F/Sa**	**M/Tu**	**W/Th**	**F/Sa**		
Visit Days →	**-14 to -1**	**1**	**3**	**5**	**8**	**10**	**12**	**85 (+3)**	**92 (+3)**
					15	**17**	**19**		
					22	**24**	**26**		
					29	**31**	**33**		
					36	**38**	**40**		
					43	**45**	**47**		
					50	**52**	**54**		
					57	**59**	**61**		
					64	**66**	**68**		
					71	**73**	**75**		
					78	**80**	**82**		
Administrative Procedures									
Informed Consent	X								
Inclusion/Exclusion Criteria	X	X[b]							
Medical History	X	X[b]							
Randomization		X							
Safety and Efficacy Evaluations									
Physical Examination	X							X	
Height	X								
Weight (estimated dry body weight)	X	X						X	
Post-dialysis weight		X						X	
12-lead Electrocardiogram[c]	X[c]	X[c]			X[c]			X[c]	
Pre-dialysis Vital Signs[d]	X	X			X[e]			X	X
Hematology, Serum Chemistry (pre-dialysis)	X	X[f]			X[f]			X[f]	
Serum Pregnancy (females of childbearing potential only)	X							X	
FSH[g]	X[g]								

PART B - Continued									
Study Procedures	**Screen**	**Treatment Period[a]**						**End of Treatment/ Early Termination**	**Follow-Up**
	Day -14 to Day -1	**Week 1**			**Week 2 to 12**				**+7 days after EOT**
		M/Tu	**W/Th**	**F/Sa**	**M/Tu**	**W/Th**	**F/Sa**		
Visit Days →	**-14 to -1**	**1**	**3**	**5**	**8**	**10**	**12**	**85 (+3)**	**92 (+3)**
					15	**17**	**19**		
					22	**24**	**26**		
					29	**31**	**33**		
					36	**38**	**40**		
					43	**45**	**47**		
					50	**52**	**54**		
					57	**59**	**61**		
					64	**66**	**68**		
					71	**73**	**75**		
					78	**80**	**82**		
Safety and Efficacy Evaluations									
Patient Self-categorization of Pruritus Disease Severity	X								
Patient training on PRO Worksheets	X[h]	X[i]							
Worst Itching Intensity NRS (daily)[j]	X	X						X	
Skindex-10 Scale, MOS Sleep Scale, 5-D Itch Scale, Patient Global Assessment of Worst Itch Severity[j]		X[j]			X[j,k]			X	
Patient Global Impression of Change								X	
Record procedural data for dialysis (including ESA and IV iron)		X	X	X	X	X	X	X	
IV administration of study drug after dialysis		X	X	X	X	X	X		

PART B - Continued									
Study Procedures	**Screen**	**Treatment Period[a]**						**End of Treatment/ Early Termination**	**Follow-Up**
	Day -14 to Day -1	**Week 1**			**Week 2 to 12**				**+7 days after EOT**
		M/Tu	**W/Th**	**F/Sa**	**M/Tu**	**W/Th**	**F/Sa**		
Visit Days →	**-14 to -1**	**1**	**3**	**5**	**8**	**10**	**12**	**85 (+3)**	**92 (+3)**
					15	**17**	**19**		
					22	**24**	**26**		
					29	**31**	**33**		
					36	**38**	**40**		
					43	**45**	**47**		
					50	**52**	**54**		
					57	**59**	**61**		
					64	**66**	**68**		
					71	**73**	**75**		
					78	**80**	**82**		
Safety and Efficacy Evaluations									
Inflammatory biomarker samples[l]		X						X	
Adverse Event Monitoring	X	X						X	X
Prior Medications	X								
Concomitant Medications[n]		X[m]			X[m]			X	X

EOT=end of treatment; ESA= erythropoiesis-stimulating agent; F=Friday; FSH=follicle-stimulating hormone; IV=intravenous; M=Monday; MOS=Medical Outcomes Study; NRS=numerical rating scale; PRO=patient-reported outcome; Sa=Saturday; Th=Thursday; Tu=Tuesday; W=Wednesday;

[a] Each visit during the Treatment Period will coincide with the patient's normal dialysis treatments.

[b] Medical history will be updated on Day 1 with any changes since the Screening Visit, and inclusion/exclusion criteria will be confirmed prior to randomization.

[c] Electrocardiogram must be performed prior to dialysis at Screening, Day 1, Day 29, and Day 85..

[d] Vital signs will be obtained in a sitting or semi-recumbent position (for at least 3 min) and will include body temperature, heart rate, and blood pressure.

[e] On Day 15, 29, and 57 only, pre-dialysis vital signs should be recorded

[f] On Day 1, 15, 29, 43, 57, and 85 only. Serum chemistry should include parathyroid hormone, pre-albumin, ferritin and transferrin saturation.
[g] Obtain on women who have been amenorrheic for at least 1 year and are between 45 and 55 years of age.
[h] Training on Worst Itching Intensity NRS only
[i] Training on Skindex-10 Scale, MOS Sleep Scale, 5-D Itch Scale, and Patient Global Impression of Worst Itch Severity scales may be performed at any time during the week prior to randomization.
[j] To be performed prior to or during dialysis, but must be completed prior to dosing.
[k] Skindex-10 Scale and 5-D Itch Scale completed on the first visit of Week 3, 5, 7, 9, and 11 (Day 15, 29, 53, 57, and 71, respectively). MOS Sleep Scale completed on the first visit of Week 4, 8, and 12 (Day 22, 50, and 78, respectively). Patient Global Impression of Worst Itch Severity completed on the first visit of Week 2, 4, 8, and 12 (Day 8, 22, 50, and 78, respectively). If the first visit of the week is missed, the patient may complete the procedures at their next visit for the same week.
[l] Biomarker samples must be collected prior to the start of dialysis.
[m] Concomitant medications will be updated on a weekly basis at the beginning of each week.

18.2 APPENDIX II Pharmacokinetic Blood Sampling Schedule

A subset of up to 40 patients (10 patients per treatment group) who consent to have blood samples taken for determining the PK profile of CR845 will be evaluated in the study. A total of 25 samples are to be collected from each patient. The timing for the collection of these samples will be according to the following schedule:

Treatment		Pharmacokinetic Samples							
				Time After Study Drug Administration (Post-dialysis)[a]					
Week	Day	Pre-dialysis[b]	Post-dialysis[c]	5 minutes	30 minutes	1 hour	2 hours	4 hours	24 hours
1	1	X	X	X	X	X	X	X	
	2								X
	3	X		X					
2	8	X		X					
4	22	X		X					
6	36	X		X					
8	50	X	X	X	X	X	X	X	
	51								X
	52	X							

a Time relative to injection of study drug (i.e., t = 0). Sample taken at 5 minutes will have a window of ± 1 minute, the 30-minute sample will have a window of ± 5 minutes, the 1-hour, 2-hour, 4-hour samples will have a window of ± 10 minutes, and the 24-hour sample will have a window of ± 1 hour.

b Sample to be collected within 30 minutes prior to start of dialysis.

c Sample to be collected within 15 minutes following the end of dialysis and prior to study drug administration.

18.3 APPENDIX III Worst Itching Intensity Numerical Rating Scale (NRS)

This is a representation of the content of the instrument to be used, but is not the actual instrument. Please refer to the Study Reference Manual for the instrument to be administered to patients and instructions.

Completed in Dialysis Unit or at Home? (please mark only one)

☐ **Dialysis Unit**

☐ **Home**

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**

Actual Date Completed: _____

Time: ☐ ☐

☐**AM** ☐**PM**

SUBJECT INITIALS

FIRST	MIDDLE	LAST

18.4 APPENDIX IV Patient Self-Categorization of Pruritus Disease Severity

This is a representation of the content of the instrument to be used, but is not the actual instrument. Please refer to the Study Reference Manual for the instrument to be administered to patients and instructions.

Patient A:

I do not generally have scratch marks on my skin.

I do not generally have a problem sleeping because of itching.

My itching does not generally make me feel agitated or sad.

Patient B:

I sometimes have scratch marks on my skin.

I sometimes have problems sleeping because of itching.

My itching can sometimes make me feel agitated or sad.

Patient C:

I often have scratch marks on my skin that may or may not bleed or get infected.

I often have a problem sleeping because of itching.

My itching often makes me feel agitated or sad.

Which of these patients are you most like? (Mark one)

- ○ Patient A
- ○ Patient B
- ○ Patient C

Mathur VS et al. CJASN 2010; 5 :1410-1419

18.5 APPENDIX V Skindex-10 Scale

This is a representation of the content of the instrument to be used, but is not the actual instrument. Please refer to the Study Reference Manual for the instrument to be administered to patients and instructions.

INSTRUCTIONS: During the past **WEEK**, how often have you been bothered by:

	0 (Never bothered)	1	2	3	4	5	6 (Always bothered)
1. Your itching	O	O	O	O	O	O	O
2. The persistence/reoccurrence of your itching	O	O	O	O	O	O	O
3. The appearance of your skin from scratching	O	O	O	O	O	O	O
4. Frustration about your itching	O	O	O	O	O	O	O
5. Being annoyed about your itching	O	O	O	O	O	O	O
6. Feeling depressed about your itching	O	O	O	O	O	O	O
7. Feeling embarrassed about your itching	O	O	O	O	O	O	O
8. The effects of your itching on your interactions with others (for example: interactions with family, friends, close relationships, etc.)	O	O	O	O	O	O	O
9. The effects of your itching on your desire to be with people	O	O	O	O	O	O	O
10. The effect of your itching making it hard to work or do what you enjoy	O	O	O	O	O	O	O

Mathur VS et al. CJASN 2010; 5 :1410-1419

18.6 APPENDIX VI Medical Outcomes Study (MOS) Sleep Scale

This is a representation of the content of the instrument to be used, but is not the actual instrument. Please refer to the Study Reference Manual for the instrument to be administered to patients and instructions.

1. How long did it usually take for you to fall asleep during the past week (Circle One)

0-15 minutes……1
16-30 minutes……...2
31-45 minutes……..…....3
46-60 minutes…….....4
More than 60 minutes……5

2. On the average, how many hours did you sleep each night during the past week?

Write the number of hours per night: ☐☐

How often during the past week did you…
(Circle one number on each line)

	All of the Time ▼	Most of the Time ▼	A Good Bit of the Time ▼	Some of the Time ▼	A Little of the Time ▼	None of the Time ▼
3. feel that your sleep was not quiet (moving restlessly, feeling tense, speaking, etc., while sleeping)?	1	2	3	4	5	6
4. get enough sleep to feel rested upon waking in the morning?	1	2	3	4	5	6
5. awaken short of breath or with a headache?	1	2	3	4	5	6
6. feel drowsy or sleepy during the day?	1	2	3	4	5	6
7. have trouble falling asleep?	1	2	3	4	5	6
8. awaken during your sleep time and have trouble falling asleep again?	1	2	3	4	5	6
9. have trouble staying awake during the day?	1	2	3	4	5	6
10. snore during your sleep?	1	2	3	4	5	6
11. take naps (5 minutes or longer) during the day?	1	2	3	4	5	6
12. get the amount of sleep you needed?	1	2	3	4	5	6

18.7 APPENDIX VII 5-D Itch Scale

This is a representation of the content of the instrument to be used, but is not the actual instrument. Please refer to the Study Reference Manual for the instrument to be administered to patients and instructions.

1. **Duration**: During the last 2 weeks, how many hours a day have you been itching?

Less than 6hrs/day	6-12 hrs/day	12-18 hrs/day	18-23 hrs/day	All day
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. **Degree**: Please rate the intensity of your itching over the past 2 weeks

Not present	Mild	Moderate	Severe	Unbearable
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. **Direction**: Over the past 2 weeks has your itching gotten better or worse compared to the previous month?

Completely resolved	Much better, but still present	Little bit better, but still present	Unchanged	Getting worse
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

4. **Disability**: Rate the impact of your itching on the following activities over the last 2 weeks

	Never affects sleep	Occasionally delays falling asleep	Frequently delays falling asleep	Delays falling asleep and occasionally wakes me up at night	Delays falling asleep and frequently wakes me up at night
Sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

	N/A	Never affects this activity	Rarely affects this activity	Occasionally affects this activity	Frequently affects this activity	Always affects this activity
Leisure/Social	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Housework/ Errands	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Work/School	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. **Distribution:** Mark whether itching has been present in the following parts of your body over the last 2 weeks. If a body part is not listed, choose the one that is closest anatomically.

	Present		Present
Head/Scalp	☐	Soles	☐
Face	☐	Palms	☐
Chest	☐	Tops of Hands/Fingers	☐
Abdomen	☐	Forearms	☐
Back	☐	Upper Arms	☐
Buttocks	☐	Points of Contact w/ Clothing	
Thighs	☐	(e.g waistband, undergarment)	☐
Lower legs	☐	Groin	☐
Tops of Feet/Toes	☐		

18.8 APPENDIX VIII Patient Global Impression of Worst Itch Severity

This is a representation of the content of the instrument to be used, but is not the actual instrument. Please refer to the Study Reference Manual for the instrument to be administered to patients and instructions.

Please choose from the following options the one that best describes your worst itch in the last 24 hours.

- ☐ None
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very severe

18.9 APPENDIX IX Patient Global Impression of Change

This is a representation of the content of the instrument to be used, but is not the actual instrument. Please refer to the Study Reference Manual for the instrument to be administered to patients and instructions.

The patient will provide their overall impression of the status of the itch related to their uremic pruritus on a 7-point scale where 1 = "Very much improved" and 7 = "Very much worse."

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

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