A MULTICENTER, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY TO EVALUATE THE SAFETY AND EFFICACY OF INTRAVENOUS CR845 IN HEMODIALYSIS PATIENTS WITH MODERATE-TO-SEVERE PRURITUS, WITH A 52-WEEK OPEN-LABEL EXTENSION

Protocol number:	CR845-CLIN3103
Phase:	3
IND number:	123140
EUDRACT number:	2018-001930-17
Investigational Product:	CR845 solution (for clinical trial use only)
Protocol version:	Version 2.2
Date:	10 September 2019
Sponsor:	Cara Therapeutics, Inc. 4 Stamford Plaza Stamford, CT 06902 (203) 406-3700

SPONSOR APPROVAL / SIGNATURE PAGE

Medical Monitor Name and Contact Information

Refer to the Investigator Site File (ISF).

INVESTIGATOR APPROVAL STATEMENT

I have read and understand the protocol (CR845-CLIN3103) and I agree that this document contains all ethical, legal, and scientific information necessary to conduct this study. I will oversee the conduct of the study as described in the protocol and any amendment(s) made to the protocol.

I agree to conduct the study as detailed herein and in compliance with the current International Council for Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice and all applicable regulatory requirements.

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

Printed Name: _____

Signature: _____

Date: _____

1.0 Protocol Synopsis

STUDY TITLE	A Multicenter, Double-blind, Randomized, Placebo-controlled Study to Evaluate the Safety and Efficacy of Intravenous CR845 in Hemodialysis Patients with Moderate-to-Severe Pruritus, with a 52-Week Open-label Extension
PROTOCOL NUMBER	CR845-CLIN3103
EUDRACT NUMBER	2018-001930-17
PHASE OF DEVELOPMENT	3
INVESTIGATIONAL PRODUCT	CR845 Solution (for clinical trial use only)
NAME OF ACTIVE INGREDIENT	CR845
ROUTE OF ADMINISTRATION	Intravenous (IV)
STUDY CENTERS	Approximately 95 US and non-US sites
OBJECTIVES	Primary Objective • To evaluate the efficacy of IV CR845 at a dose of 0.5 mcg/kg compared to placebo in reducing the intensity of itch in hemodialysis patients with moderate-to-severe pruritus. Secondary Objectives • To evaluate the efficacy of IV CR845 at a dose of 0.5 mcg/kg compared to placebo in improving itch-related quality-of-life measures in hemodialysis patients with moderate-to-severe pruritus. • To evaluate the safety of IV CR845 at a dose of 0.5 mcg/kg in hemodialysis patients with moderate-to-severe pruritus.
NUMBER OF PATIENTS	The planned sample size is 350 (175 per treatment group) male and female hemodialysis patients with moderate-to-severe pruritus. The sample size may be increased to 500 patients (250 per treatment group) based on the results of a planned interim assessment conducted when approximately 50% of the planned 350 patients have been randomized and have either completed the 12-week Treatment Period or have discontinued study drug early.
STUDY POPULATION	**Inclusion Criteria:** To be eligible for inclusion into the Double-blind Phase of the study, a patient must meet the following criteria: 1. Willing and able to provide written informed consent prior to participating in this study;

	2. Able to communicate clearly with the Investigator and staff, able to understand the study procedures, and able and willing to comply with the study requirements, including providing written responses to questionaires; 3. Male or female between 18 and 85 years of age inclusive; **Note**: Subjects in Korea, must be male or female between 19 and 85 years of age, inclusive. 4. Has end-stage renal disease (ESRD) and has 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 or electrolyte excesses may be enrolled as long as it is anticipated that no more than 1 such treatment will be required in any given week and no more than 4 occasions during the 12-week double-blind period. Patients routinely on 4 dialyses a week will not be eligible. **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. **Note 3**: Patients receiving alternate dialysis modalities such as nocturnal dialysis will not be eligible. 5. If female, is not pregnant or nursing during any period of the study; 6. If female: a. Is surgically sterile; or b. Has been amenorrhoeic for at least 1 year and is over the age of 55 years; or c. Has a negative serum pregnancy test at screening and agrees to use acceptable contraceptive measures (eg, hormonal contraceptives, barrier with spermicide, intrauterine device, vasectomized partner, or abstinence) from the time of informed consent until 7 days after the last dose of study drug; 7. If male, agrees not to donate sperm after the first dose of study drug until 7 days after the last dose of study drug, and agrees to use a condom with spermicide or abstain from heterosexual intercourse during the study until 7 days after the last dose of study drug. (Note: No restrictions are required for a vasectomized male provided his vasectomy was performed ≥4 months prior to screening); 8. Has a prescription dry body weight between 40.0 and 135.0 kg, inclusive;

	9. Has 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; 10. Prior to randomization: a. Has completed at least four out of eight Worst Itching Intensity Numerical Rating Scale (NRS) worksheets from the start of the 7-day Run-in Period up to and including the pre-randomization assessment on Day 1; b. Has a mean baseline Worst Itching Intensity NRS score ≥5, defined as the average of all non-missing scores reported from the start of the 7-day Run-in Period up to and including the pre-randomization assessment on Day 1. **To be eligible for inclusion into the Open-label Extension Phase of the study, each patient will have to fulfill the additional following criteria at the time of entry into the Open-label Extension Phase:** 11. Has received at least 30 doses of the planned 36 doses of study drug during the Double-blind Phase of this study; 12. Has a prescription dry body weight ≥40 kg; 13. Continues to meet inclusion criteria 1 through 7. **Exclusion Criteria:** A patient will be excluded from the Double-blind Phase of the study if any of the following criteria are met: 1. Known noncompliance with dialysis treatment that in the opinion of the Investigator would impede completion or validity of the study; 2. Scheduled 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. Has a concomitant disease or a history of any medical condition that, in the opinion of the Investigator, could pose undue risk to the patient, impede completion of the study procedures, or would compromise the validity of the study measurements, including, but not limited to: a. Known or suspected history of alcohol, narcotic, or other drug abuse, or substance dependence within 12 months prior to screening; b. Significant systolic or diastolic heart failure (eg, New York Heart Association Class IV congestive heart failure [Appendix 1, Section 14.1]); c. Severe mental illness or cognitive impairment (eg, dementia);

	d. Any other relevant acute or chronic medical or neuropsychiatric condition within 3 months prior to screening (eg, diagnosis of encephalopathy, coma, delirium); 5. New or change of treatment received for itch including antihistamines and corticosteroids (oral, IV, or topical) within 14 days prior to screening; 6. New or change of prescription for opioids, gabapentin, or pregabalin within 14 days prior to screening; 7. Received another investigational drug within 30 days prior to the start of screening or is planning to participate in another clinical study while enrolled in this study; 8. In the opinion of the Investigator, has pruritus attributed to a cause other than ESRD or its complications (eg, patients with concomitant pruritic dermatological disease or cholestatic liver disease) (Note: Patients whose pruritus is attributed to ESRD complications, such as hyperparathyroidism, hyperphosphatemia, anemia, or the dialysis procedure or prescription may be enrolled); 9. Has localized itch restricted to the palms of the hands; 10. Has pruritus only during the dialysis session (by patient report); 11. Is receiving ongoing ultraviolet B treatment and anticipates receiving such treatment during the study; 12. Participated in a previous clinical study with CR845. **A patient will be excluded from the Open-label Extension Phase of the study if any of the additional following criteria are met at the time of entry into the Open-label Extension Phase:** 13. Completed the Double-blind Phase of this study but exhibited adverse events during the course of the Treatment Period that may preclude continued exposure to the study drug; 14. Was noncompliant with protocol procedures during the Double-blind Phase of this study which is indicative of an inability to follow protocol procedures; 15. Has developed a concomitant disease or any medical condition that, in the opinion of the Investigator, could pose undue risk to the patient, impede completion of the study procedures, or would compromise the validity of the study measurements.
STUDY DESIGN	This is a multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of IV CR845 at a dose of 0.5 mcg/kg administered after each dialysis session. The study includes a Double-blind Phase, an Open-label Extension Phase, and a Follow-up Period. ***Double-blind Phase***

	The Double-blind Phase of the study will consist of a Screening Visit, a 7-day Run-in Period and a 12-week Double-blind Treatment Period. Informed consent will be obtained prior to performing any study-specific procedures. The Screening Visit will occur within 7 to 28 days prior to randomization to assess eligibility. The site has the option to conduct the Screening Visit within the Run-in Period at the discretion of the Investigator. Eligible patients will complete a 7-day Run-in Period during the week prior to randomization to confirm eligibility, preferably starting on the first dialysis session of that week (ie, Monday for patients on a Monday-Wednesday-Friday dialysis schedule or Tuesday for patients on a Tuesday-Thursday-Saturday dialysis schedule). The purpose of the Run-in Period is to confirm that each patient has moderate-to-severe pruritus (ie, weekly average worst itch score ≥5), as measured by the patient-daily reported 24-hour Worst Itching Intensity NRS, and to establish a baseline itch intensity. Patients must not be informed that they need to report a weekly average worst itch score ≥5 to be enrolled in the study. During the first visit of the Run-in Period, patients will be trained on completion of the 24-hour Worst Itching Intensity NRS and will start the reporting of their Worst Itching Intensity NRS daily score. For consistency, patients will be requested to complete the NRS worksheets (either at home or in the dialysis unit, as required) each day at a similar time of day around the normal start time of their dialysis. Patients will be trained on other itch-related patient-reported outcome (PRO) worksheets during the Run-in Period or on Day 1 of the Double-blind Treatment Period. If patients continue to meet all inclusion and no exclusion criteria at the end of the 7-day Run-in Period, they will be randomized into the Double-blind Treatment Period in a 1:1 ratio to receive either IV CR845 0.5 mcg/kg or placebo. Patients will be stratified according to their use or non-use of concomitant medications to treat their itch during the week prior to randomization (Run-in Period) as well as the presence or absence of specific medical conditions. These specific medical conditions include: • History of fall or fracture (related to fall) • Confusional state or mental status change or altered mental status or disorientation • Gait disturbance or movement disorder Day 1 of the Double-blind Treatment Period will be defined as the day of administration of the first dose of study drug and will occur preferably on the first dialysis session of the first treatment week (ie, Monday for patients on a Monday-Wednesday-Friday dialysis schedule, or Tuesday for patients on a Tuesday-Thursday-Saturday dialysis schedule). Patients will be administered CR845 or matched placebo as an IV bolus after the end of each dialysis session during the

	12-week Double-blind Treatment Period. Each patient is to receive CR845 or placebo 3 times weekly for a total of up to 36 doses. During the Double-blind Treatment Period, patients will continue to report their daily Worst Itching Intensity NRS score over the previous 24 hours. In addition, during selected study visits (Day 1 and first day of Weeks 5, 9, 11, and 13 [ie, Days 29, 57, 71, and 85]), they will complete other PRO measures (such as Skindex-10 Scale, 5-D Itch Scale, and Patient Global Impression of Change). Patients will be instructed to record patient-reported outcome measurements, including Worst Itching Intensity NRS scores, at a similar time of day, whether in the dialysis unit (on dialysis days) or at home (on non-dialysis days). Blood samples for clinical laboratory tests will be collected at the Screening Visit and on Days 1 and 85. Blood samples for biomarkers will be collected on Days 1 and 85. Electrocardiograms (ECGs) will be monitored at the Screening Visit and on Day 85. Vital signs will be monitored periodically, and adverse events and concomitant medications will be continuously recorded during the Double-blind Phase. Use of antipruritic medications and missed dialysis will be recorded throughout the Double-blind Phase. A Structured Safety Evaluation will be performed once during the Run-in Period and weekly (preferably on Wednesday/Thursday) during the Double-blind Treatment Period. The Structured Safety Evaluation is performed by study staff using a list of specific signs/symptoms (eg, mental status change, falls, gait disturbance). ***Open-label Extension Phase*** Patients who received at least 30 doses of study drug (either active or placebo) during the 12-week Double-blind Treatment Period and continue to meet other eligibility criteria will be eligible to receive open-label CR845 for an additional 52 weeks. Each patient will receive CR845 at a dose of 0.5 mcg/kg after each dialysis session, 3 times per week for up to 52 weeks, regardless of whether they had been previously administered placebo or CR845. Prescription dry body weight will be recorded at the start of and every 12 weeks during the Open-label Extension Phase; if there is a ±10% or more change from the prescription dry body weight recorded at Screening, then the CR845 dose will be adjusted according to the newly recorded dry body weight. The first visit and first dosing for the Open-label Extension Phase of the study will occur immediately on the day of the last visit of the Double-blind Treatment Period or up to 1 week following the Double-blind Treatment Period. Patients will complete the 5-D Itch Scale during Weeks 4, 8, 12, 24, 36, and 52 (preferably at the end of the specified weeks). Clinical laboratory tests, vital signs, adverse events, and concomitant medications will be monitored throughout the Open-label Treatment Period. Blood samples for inflammatory biomarkers will be collected

	periodically until the Open-label End-of-Treatment or Early Termination Visit. ECGs will be monitored at the Open-label End-of-Treatment or Early Termination Visit. The number and reason(s) for missed dialysis as well as the use of antipruritic medications will be recorded throughout the Open-label Extension Phase. The last dose of open-label study drug will be administered at the last dialysis visit on Week 52, or Early Termination. ***Follow-up Period*** A final safety Follow-up Visit will be conducted 7-10 days after the End-of-Treatment Visit of the Double-blind Treatment Period for patients not participating in the Open-label Extension Phase, after the End-of-Treatment Visit of the Open-label Extension Phase, or after the Early Termination Visit during either the Double-blind Treatment Period or the Open-label Extension Phase.
STUDY DRUG	Study drug will be supplied in glass vials containing an extractable volume of at least 1.3 mL of CR845 at a concentration of 0.05 mg/mL in 0.04M isotonic acetate buffer, pH 4.5.
REFERENCE PRODUCT	Matching placebo (0.04M isotonic acetate buffer, pH 4.5) will be provided in glass vials containing an extractable volume of at least 1.3 mL.
TREATMENT REGIMENS	Patients will be administered CR845 0.5 mcg/kg or placebo as a single IV bolus 3 times a week after each dialysis session for 12 weeks during the Double-blind Treatment Period. During the Open-label Treatment Period, patients will be administered CR845 0.5 mcg/kg as a single IV bolus 3 times a week after each dialysis session for up to 52 weeks.
STUDY DURATION	***Double-blind Phase:*** Screening Period: up to 4 weeks (Screening Visit may occur during Run-in Period at the discretion of Investigator) inclusive of the 7-day Run-in Period Double-blind Treatment Period: 12 weeks ***Open-label Extension Phase:*** up to 52 weeks ***Follow-up Period:*** 7-10 days Total study duration for a single patient: up to approximately 70 weeks
STUDY ENDPOINTS	<u>Efficacy Endpoints</u> **Primary Efficacy Endpoint** • Proportion of patients achieving at least a 3-point improvement from baseline with respect to the weekly mean of the daily 24-hour Worst Itching Intensity NRS score at Week 12 of the Double-blind Treatment Period

	Secondary Efficacy Endpoints • Proportion of patients achieving ≥4-point improvement from baseline with respect to the weekly mean of the daily 24-hour Worst Itching Intensity NRS at Week 12 of the Double-blind Treatment Period. • Proportion of patients achieving ≥3-point improvement from baseline with respect to the weekly mean of the daily 24-hour Worst Itching Intensity NRS at Week 8 of the Double-blind Treatment Period. • Proportion of patients achieving ≥3-point improvement from baseline with respect to the weekly mean of the daily 24-hour Worst Itching Intensity NRS at Week 4 of the Double-blind Treatment Period. • Proportion of patients achieving ≥4-point improvement from baseline with respect to the weekly mean of the daily 24-hour Worst Itching Intensity NRS at Week 8 of the Double-blind Treatment Period. • Proportion of patients achieving ≥4-point improvement from baseline with respect to the weekly mean of the daily 24-hour Worst Itching Intensity NRS at Week 4 of the Double-blind Treatment Period. • Change from baseline in itch-related quality of life at the end of Week 12 of the Double-blind Treatment Period, as assessed by the Skindex-10 Scale total score • Change from baseline in itch-related quality of life at the end of Week 12 of the Double-blind Treatment Period, as assessed by the 5-D Itch Scale total score Additional efficacy endpoints are described in Section 8.7.4. Safety Endpoints The safety endpoints used to evaluate the overall safety and tolerability of CR845 will be adverse events, ECG, vital signs, and clinical safety laboratory evaluations.
INTERIM ASSESSMENT (Double-blind Phase)	Safety data will be reviewed on an ongoing basis by the Sponsor and a Data Safety Monitoring Board (DSMB). The operation of the DSMB will be governed by a charter that will describe the group's meeting frequency, procedures, and requirements for reporting its observations to the Sponsor. The DSMB will not be part of the study team and will receive unblinded safety results on a regular basis. A single interim assessment for sample size re-estimation is planned after approximately 50% of the first 350 randomized patients either complete the 12-week Double-blind Treatment Period or discontinue study drug prematurely. The interim assessment will be conducted by an Independent Data Monitoring Committee (IDMC). Members of the IDMC will not participate in the DSMB and will not be members of the study team. During the interim assessment, the study team will remain

	blinded to the data; however, the IDMC will receive unblinded summary results to implement the decision rule for sample size re-estimation. The IDMC will only communicate the decision to either keep the original sample size or to increase it; no other results will be provided to blinded staff. The DSMB will be made aware of the decision, but not given the results that were the basis of the decision.
STATISTICAL ANALYSIS	**Analysis Populations** The Enrolled Population is defined as the group of patients who sign informed consent. The intent-to-treat (ITT) Population is defined as the group of patients who are randomized to a treatment group. The Double-blind Safety Population is defined as the group of randomized patients who received at least 1 dose of study drug during the Double-blind Treatment Period. Following the intent-to-treat principle, patients in the ITT Population will be analyzed according to their randomized treatment, regardless of the actual treatment received. Patients in the Double-blind Safety Analysis Population will be analyzed according to the actual treatment received. The Double-blind Safety Population will be used to analyze all safety endpoints collected during the Double-blind Phase, while the ITT Population will be used to analyze all efficacy endpoints collected during the Double-blind Phase. The Per-Protocol Population is defined as the subset of patients in the ITT Population who do not have any major protocol deviations that could affect the efficacy analyses of the double-blind data. Inclusion in the Per-Protocol Population will be determined prior to unblinding the data and will be detailed in the statistical analysis plan. The Open-label Safety Population is defined as the group of patients who receive at least 1 dose of study drug in the Open-label Extension Phase. The Open-label Safety Population will be used to analyze all safety endpoints collected during the Open-label Extension Phase, and during exposure to CR845 combining data from both the Double-blind and the Open-label Extension Phases. **Safety Analyses** Safety data will be summarized descriptively. No inferential statistics are planned. Analyses of safety data will include summaries of treatment-emergent adverse events including Adverse Events of Special Interest (AESI), serious adverse events, and adverse events resulting in study drug discontinuation. Vital signs, chemistry and hematology data, and ECG data will be presented by visit as applicable, in addition to change from baseline.

	Efficacy Analyses (Double-blind Treatment Period) All efficacy analyses will be conducted on the ITT Population. An analysis of the primary and secondary efficacy variables for the Per-Protocol Population will also be performed. *Primary Efficacy Endpoint* The primary efficacy endpoint is defined as the proportion of patients achieving at least a 3-point improvement from baseline with respect to the weekly mean of the daily 24-hour Worst Itching Intensity NRS score at Week 12 (Days 79-85) of the Double-blind Treatment Period. 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 during the Double-blind Treatment Period (eg, Days 2 to 8, Days 9 to 15, Days 16 to 22, … Days 79 to 85) 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 24-hour Worst Itching Intensity NRS scores collected over the Run-in Period, including pre-randomization assessments collected on Day 1. In the primary efficacy analysis, missing NRS data will be imputed using a multiple imputation (MI) approach, assuming that patients who discontinue double-blind treatment early would have similar Worst Itching Intensity NRS scores as other patients in their respective treatment arm that have complete data: • Intermittent missing NRS scores 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. • NRS scores missing after patients discontinue study drug early will then be multiply imputed with the SAS MI procedure using a method appropriate for monotone missingness (eg, regression statement). • The proportion of patients who have an improvement from baseline with respect to the weekly mean of the daily 24-hour Worst Itching Intensity NRS score ≥ 3 points will be calculated for each imputed dataset. Differences between CR845 0.5 mcg/kg and placebo with respect to the primary endpoint will be compared using a logistic regression model containing terms for treatment group, baseline NRS score, use of prior anti-itch medication, presence of specific medical conditions, and country/region. • Results of the logistic regression on the multiply imputed data sets will be summarized by the SAS MIANALYZE procedure.

	Sensitivity analyses of the primary efficacy endpoint will be conducted to evaluate the robustness of study results under different assumptions and imputation algorithms (Section 8.7.1). *Secondary Efficacy Endpoints* The proportion of patients achieving ≥4-point improvement from baseline at Week 12 of the Double-blind Treatment Period, the proportion of patients achieving ≥3-point improvement from baseline at Week 8 and Week 4, and the proportion of patients achieving ≥4-point improvement from baseline at Week 8 and Week 4 with respect to the weekly mean of the daily 24-hour Worst Itching Intensity NRS will be analyzed following a similar methodology to the one employed in the primary analysis of the primary endpoint. The Skindex-10 Scale total score and the 5-D Itch Scale total score change from baseline at Week 12 will be analyzed using an analysis of covariance (ANCOVA) model that contains treatment as fixed effect, with baseline score, region, and the randomization stratification variables as covariates. For each domain in each questionnaire, missing values at Week 12 will be imputed using a MI approach, assuming that patients who discontinue double-blind treatment early would have similar domain scores as other patients in their respective treatment arm that have complete data: • Intermittent missing scores 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. • The monotone missing values will then be multiply imputed with the SAS MI procedure using the monotone regression method. It is important to note that, in HD patients, the study drug administered during the last dialysis of a particular week is not cleared until the first dialysis of the next week. Therefore, measurements that would reflect treatment effect at the end of a specific week (eg. Week 4) will actually be collected during the first day of the next week (eg. Week 5). *Hypothesis Testing Strategy* Testing of the primary efficacy endpoint will be 2-sided and conducted at the 5% error level. The study will be considered positive if the null hypothesis of no treatment difference in the primary efficacy analysis of the primary endpoint (proportion of patients with a ≥3-point improvement from baseline at Week 12 of the Double-blind Treatment Period with respect to the Worst Itching Intensity NRS) is rejected in favor of the alternative that patients randomized to CR845 experience significantly less itching compared to patients randomized to placebo.

	To protect the Type 1 error, a gate-keeping strategy will be implemented. Although the p-values corresponding to the hypothesis testing of the secondary variables will be reported, they will only be considered inferential if the primary analysis is statistically significant. Testing of the secondary efficacy endpoints will be performed sequentially at a 2-sided 5% error level in the order specified below. If the test of an endpoint in the sequence is not statistically significant, the p-value for the tests corresponding to the remaining endpoints in the sequence will not be considered inferential and the null hypotheses for the subsequent tests will not be rejected. 1. Proportion of patients achieving ≥4-point improvement from baseline with respect to the weekly mean of the daily 24-hour Worst Itching Intensity NRS at Week 12 of the Double-blind Treatment Period 2. Proportion of patients achieving ≥3-point improvement from baseline with respect to the weekly mean of the daily 24-hour Worst Itching Intensity NRS at Week 8 of the Double-blind Treatment Period 3. Proportion of patients achieving ≥3-point improvement from baseline with respect to the weekly mean of the daily 24-hour Worst Itching Intensity NRS at Week 4 of the Double-blind Treatment Period 4. Proportion of patients achieving ≥4-point improvement from baseline with respect to the weekly mean of the daily 24-hour Worst Itching Intensity NRS at Week 8 of the Double-blind Treatment Period 5. Proportion of patients achieving ≥4-point improvement from baseline with respect to the weekly mean of the daily 24-hour Worst Itching Intensity NRS at Week 4 of the Double-blind Treatment Period 6. Change from baseline in Skindex-10 Scale total score at Week 12 of the Double-blind Treatment Period 7. Change from baseline in 5-D Itch Scale total score at Week 12 of the Double-blind Treatment Period Details and methods of analysis are found in Section 8.0 and will be described further in the statistical analysis plan.

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3.0 List of Abbreviations

AESI	adverse event of special interest
ATC	Anatomical Therapeutic Chemical
CFR	Code of Federal Regulations
CI	confidence interval
CNS	Central nervous system
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
ESRD	end-stage renal disease
FDA	Food and Drug Administration
GCP	Good Clinical Practice
H	above the laboratory parameter's reference range
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IL	interleukin
IND	Investigational New Drug
IRB	Institutional Review Board
ISF	Investigator Site File
ITT	intent-to-treat
IV	intravenous
IVRS/IWRS	interactive voice or web response system
KOR	kappa-opioid receptor
L	below the laboratory parameter's reference range
LS	least squares
MAR	missing at random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MMRM	mixed effects model with repeated measures
MNAR	missing not at random
N	within the laboratory parameter's reference range
NRS	numerical rating scale
PRO	patient-reported outcome
SAE	serious adverse event
SAP	statistical analysis plan
SE	standard error
SOC	System Organ Class
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

Abbreviations that occur only in tables or figures are defined within the appropriate table or figure.

4.0 Introduction

4.1 Background and Rationale

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

Opioid receptors are involved in the modulation of itch and pain signals and consist of 3 subtypes: mu, kappa, and delta. These receptor subtypes are found in the central nervous system (CNS), in peripheral nervous system tissues, such as skin and viscera, and in the immune system (see Investigator's Brochure for references and further details). CR845 was designed to only activate KORs located primarily in the peripheral nervous system, which are known to modulate itch, pain, and inflammatory signals, without producing the side effects associated with the activation of mu-opioid receptors, such as respiratory depression, abuse liability, and constipation.

CR845 is a potent and selective KOR agonist with no activity at mu- and delta-opioid receptors or other receptors, ion channels, or transporters. CR845's unique peptidic structure significantly differs from other small molecule KOR agonists developed to date, which, for the most part, are CNS-active. Being a hydrophilic peptide, CR845 has limited membrane permeability by passive diffusion, which limits its access to the CNS. Since CR845 does not activate receptors other than KORs and does not readily enter the CNS, it is expected to be safer and better tolerated than other opioid agonists, including CNS active kappa agonists. Thus far, CR845 has shown no abuse properties and no respiratory depression effects (see Investigator's Brochure for details).

Uremic pruritus is a chronic, unremitting, and highly bothersome condition in patients with chronic kidney disease that adversely affects sleep, mood, and ability to socialize [Kumagai 2010]. Patients with uremic pruritus frequently exhibit considerable mechanical skin damage because of continuous scratching with excoriations, superimposed infections, and chronic lesions of prurigo nodularis or skin lichenification often occurring. The mechanical skin damage can become an additional source of itching. Consequently, these patients are at increased risk of related morbidities associated with infection, eg, cellulitis, sepsis, bacteremia, cutaneous infections, and infections of the dialysis access, and are at higher mortality risk (>15%) [Pisoni 2006; Narita 2006]. Large multinational studies (Dialysis Outcomes and Practice Patterns) and studies based in the United States have demonstrated that approximately 30 to 40% of hemodialysis patients have moderate-to-severe pruritus. There are no approved treatments for this condition in the United States and current off-label therapies are unable to successfully treat uremic pruritus.

Although the pathophysiology of moderate-to-severe pruritus in hemodialysis patients is not well understood, there is increasing evidence that it is likely multifactorial and that an

immune system dysfunction (including elevated proinflammatory activity) and imbalance in the endogenous opioid system (with over-expression of mu-opioid receptors in dermal cells and lymphocytes and concomitant downregulation of KORs) are involved [Kimmel 2006; Narita 2006; Phan 2012; Patel 2007; Mettang 2002; Tey 2011].

In nonclinical studies, CR845 has been shown to exhibit antipruritic and anti-inflammatory properties [Investigator's Brochure]. Thus, CR845 is intended to reduce the severity of itching in hemodialysis patients and thereby decrease the likelihood of developing additional serious conditions associated with uremic pruritus.

4.2 Clinical Experience

4.2.1 Overall Exposure

As of the writing of this protocol, the intravenous (IV) formulation of CR845 has been evaluated in 722 patients and healthy volunteers across eight Phase 1 studies (including 2 studies conducted in Japan), three Phase 2 studies for the relief of moderate-to-severe, acute postoperative pain, and two Phase 2 studies for the relief of moderate-to-severe pruritus in hemodialysis patients. In the United States, CR845 has been evaluated both as an IV bolus and a 15-minute infusion of single or repeated doses ranging from 0.5 to 40 mcg/kg.

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

4.2.2 Safety in Hemodialysis Patients

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

CR845-CLIN2101 evaluated the safety, pharmacokinetics, and efficacy of repeated IV doses of CR845 compared to placebo over an 8-week treatment period in 174 hemodialysis patients. As expected with patients on hemodialysis, a significant number of the reported serious adverse events (SAEs) were considered not treatment-related, but related to the disease and/or comorbid conditions. There were 31 (17.8%) of

174 patients randomized and treated in the study who had treatment-emergent SAEs. Of the 31 SAE reports, 4 (9%) occurred in 45 placebo-treated patients and 27 (21%) in 129 CR845-treated patients. Only 1 SAE of mental status changes (moderate in severity) in a patient who received CR845 1.5 mcg/kg IV was considered by the Investigator to be probably related to study drug. However, based on the Sponsor's medical review, an alternate etiology of urgent/emergent hypertension offers a more plausible explanation for the acute change in mental status. There were 4 patient deaths (1 in placebo group, 1 in CR845 0.5 mcg/kg group, and 2 in CR845 1.5 mcg/kg group; 2.3% of the total study population) in the study, all of which were considered not related to the study drug.In patients with normal renal function, CR845 can cause free-water diuresis (aquaresis) and increased serum sodium. However, as would be expected in patients undergoing dialysis in whom there are few functioning nephrons, there was no evidence of aquaresis or significant increases in serum sodium concentrations. There were no adverse trends in clinical chemistry or hematology values (drawn pre-dialysis), including no apparent differences between the placebo and CR845 groups in serum sodium. There were no discernable differences between treatment groups in vital sign results. Of particular note, among patients receiving CR845, there was no apparent reduction in blood pressure or respiratory rate following dosing.

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

4.2.3 Efficacy of CR845 in Hemodialysis Patients with Uremic Pruritus

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

CR845-CLIN2005 (Part B) included 65 hemodialysis patients with moderate-to-severe uremic pruritus who received either IV CR845 1.0 mcg/kg (n=33) or placebo (n=32) 3 times per week for 2 weeks, after each hemodialysis session. CR845 significantly decreased itching intensity compared with placebo (p=0.016), as measured by a visual analog scale (VAS) and significantly improved quality of life related to itching (Skindex-10 Scale) (see Investigator's Brochure for details). Furthermore, CR845-treated patients exhibited statistically significant reductions in both daytime (p=0.03) and nighttime (p=0.007) worst itching scores compared with placebo, and the reduction in itching intensity scores was similar on dialysis and nondialysis days. The mean change from baseline VAS curves over time showed numerical separation between the treatment groups within the first week of treatment.

CR845-CLIN2101 evaluated the safety, pharmacokinetics, and efficacy of repeated IV doses of CR845 compared to placebo over an 8-week treatment period in 174 hemodialysis patients experiencing moderate-to-severe uremic pruritus daily or near-daily for 4.4 years on average. The study was conducted at 33 dialysis centers and assessed the effect of 3 doses of CR845 (ie, 0.5 mcg/kg, n=44; 1 mcg/kg, n=41 and

1.5 mcg/kg, n=44) or placebo (n=45) administered at the end of each dialysis session (ie, 3 times/week). The primary efficacy endpoint for Study CR845-CLIN2101 was based on itch intensity measurement and defined as the change from a 1-week baseline recorded prior to the start of study drug to the last week of the 8-week treatment period with respect to the weekly mean of the daily 24-hour Worst Itching Intensity numerical rating scale (NRS) score. The least squares (LS) mean (±standard error [SE]) treatment group difference from placebo at Week 8 across all CR845 doses was -1.3 (±0.41) (95% confidence interval [CI]: -2.1 to -0.5) (p=0.002) with an average NRS score reduction from baseline of -3.2 (±0.22) (LS mean ±SE) and 95% CI ranging from -3.7 to -2.8. Examination of the individual CR845 dose group results for the Full Analysis Population indicates that a substantial improvement over placebo was observed with all 3 doses. These differences from placebo were statistically significant for the lower dose group of 0.5 mcg/kg (p<0.001) and the 1.5 mcg/kg group (p=0.019), with an effect size estimated as 0.82, 0.39, and 0.62 for the 0.5, 1.0, and 1.5 mcg/kg doses, respectively. Average reduction from baseline (LS mean ± SE) ranged from -2.8 (±0.38) in the 1.0 mcg/kg dose group (95% CI ranging from -3.5 to -2.0) to -3.8 (±0.38) in the 0.5 mcg/kg dose group (95% CI ranging from -4.5 to -3.1).

4.2.4 Pharmacokinetics in Hemodialysis Patients

CR845 is eliminated primarily through the kidney and no major metabolites have been identified in humans. Consequently, total body clearance of CR845 in patients with severe renal impairment is reduced relative to healthy, matched, control patients (CR845-CLIN1005) such that plasma levels of CR845 remain relatively constant until cleared during dialysis in hemodialysis patients (CR845-CLIN1003 and CR845-CLIN2005 [Part A]). Half-life ranges between 26 and 34 hours in hemodialysis patients compared to a typical range of 2 to 3 hours in patients 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 profile, CR845 does not need to be administered more than 3 times a week after each hemodialysis session, which is convenient for this patient population and ensures treatment compliance in a population already burdened with complex medication schedules.

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

4.3 Summary of Potential Risks and Benefits

During preclinical development, no specific safety findings to preclude the use of CR845 in humans were observed. During early clinical development, IV CR845 was

administered to healthy volunteers; patients with mild, moderate, or severe renal impairment, including end-stage renal disease (ESRD) and hemodialysis patients; recreational poly-drug users; and postsurgical patients. The effects of CR845 have been shown to be in line with the underlying pharmacological mechanism of KOR activity. Consistent with the nonclinical abuse liability studies conducted to date, the results of an abuse-potential study in humans indicated that CR845 appears to present a low risk for abuse potential in humans in comparison to currently clinically used opioids.

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

5.0 Objectives

Primary Objective

- To evaluate the efficacy of IV CR845 at a dose of 0.5 mcg/kg compared to placebo in reducing the intensity of itch in hemodialysis patients with moderate-to-severe pruritus.

Secondary Objectives

- To evaluate the efficacy of IV CR845 at a dose of 0.5 mcg/kg compared to placebo in improving itch-related quality-of-life measures in hemodialysis patients with moderate-to-severe pruritus.
- To evaluate the safety of IV CR845 at a dose of 0.5 mcg/kg in hemodialysis patients with moderate-to-severe pruritus.

6.0 Investigational Plan

6.1 Overall Study Design and Plan: Description

This is a multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of IV CR845 at a dose of 0.5 mcg/kg administered after each dialysis session. The study includes a Double-blind Phase and an Open-label Extension Phase. CR845 will be evaluated relative to placebo over a 12-week Double-blind Treatment Period in hemodialysis patients with moderate-to-severe pruritus. At the end of the Double-blind Treatment Period, patients who received at least 30 doses of study drug during the 12-week Double-blind Treatment Period will be eligible to receive open-label CR845 for an additional 52 weeks. A follow-up visit will be conducted 7-10 days after the last study visit on treatment or after early termination.

6.1.1 Double-blind Phase

The Double-blind Phase of the study will consist of a Screening Visit, a 7-day Run-in Period, and a 12-week Double-blind Treatment Period. Informed consent will be obtained prior to performing any study-specific procedures. The Screening Visit will occur within 7 to 28 days prior to randomization in order to assess eligibility. The Screening Visit can be conducted during the Run-in Period at the discretion of the Investigator.

6.1.1.1 Screening Visit

During the Screening Visit, patients will sign the Informed Consent, and will be evaluated for eligibility by assessment of inclusion/exclusion criteria, medical history, physical examination, prescription dry body weight, pre-dialysis 12-lead electrocardiogram, pre-dialysis vital signs, pre-dialysis hematology and serum chemistry, adverse events, and prior medications.

Serum pregnancy test for females of childbearing potential must be performed within 7 days prior to the first study dose.

During Screening and before the first visit of the Run-in Period, patients will be trained on completion of the 24-hour Worst Itching Intensity NRS scale. Patients may also be trained on other patient-reported outcome (PRO) worksheets during Screening (ie, Skindex-10 scale, 5-D itch scale and PGIC).

6.1.1.2 Run-in Period

Eligible patients will complete a 7-day Run-in Period during the week prior to randomization to confirm eligibility, preferably starting on the first dialysis session of that week (ie, Monday for patients on a Monday-Wednesday-Friday dialysis schedule or Tuesday for patients on a Tuesday-Thursday-Saturday dialysis schedule). The purpose of the Run-in Period will be to confirm that each patient has moderate-to-severe pruritus (ie, weekly average score ≥5), as measured by the 24-hour Worst Itching Intensity NRS,

and to establish a baseline itch intensity. These criteria for eligibility should not be communicated to the patients. This period will also be used to record each patient's use of itch medications.

During the first visit of the Run-in Period, patients will start the reporting of their Worst Itching Intensity NRS daily score. Patients may continue to be trained on PRO worksheets during the Run-in Period.

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.

A Structured Safety Evaluation will be performed during the Run-in Period (preferably on Wednesday/Thursday). The Structured Safety Evaluation is performed by study staff using a list of specific signs/symptoms (eg, mental status change, falls, gait disturbance).

6.1.1.3 Double-blind Treatment Period

If patients continue to meet all inclusion and no exclusion criteria at the end of the 7-day Run-in Period, they will be randomized into the Double-blind Treatment Period in a 1:1 ratio to receive either IV CR845 0.5 mcg/kg or placebo. Patients will be stratified according to their use or non-use of concomitant medications to treat their itch as well as the presence or absence of specific medical conditions.

Day 1 of the Double-blind Treatment Period will be defined as the day of administration of the first dose of study drug and will occur preferably on the first dialysis day of the first treatment week (ie, Monday for patients on a Monday-Wednesday-Friday dialysis schedule or Tuesday for patients on a Tuesday-Thursday-Saturday dialysis schedule).

Patients will be administered CR845 or matched placebo as an IV bolus after the end of each dialysis session during the 12-week Double-blind Treatment Period so that each patient will receive CR845 or placebo 3 times weekly for a total of up to 36 doses.

During the Double-blind Treatment Period, patients will continue to report their Worst Itching Intensity NRS score on a daily basis, covering the previous 24 hours. In addition, during selected study visits (Day 1 and first day of Weeks 5, 9, 11, and 13 [ie, Days 29, 57, 71, and 85]), they will complete other PRO measures (such as Skindex-10 Scale, 5-D Itch Scale, and Patient Global Impression of Change). Patients will be instructed to record patient-reported outcome measurements, including Worst Itching Intensity NRS scores, at a similar time of day, whether in the dialysis unit (on dialysis days) or at home (on non-dialysis days).

Blood samples for inflammatory biomarkers will be collected for all randomized patients prior to dialysis on Day 1 and prior to the last dialysis at the End-of-Treatment Visit for the Double-blind Treatment Period (Day 85).

Clinical laboratory tests and vital signs will be monitored periodically, and adverse events and concomitant medications will be continuously recorded during the Double-

blind Treatment Period. Electrocardiograms (ECGs) will be monitored at the Screening Visit and Day 85 or Early Termination Visit.

The number and reason(s) for missed dialysis as well as the use of antipruritic medications will be recorded throughout the study.

A Structured Safety Evaluation will be performed weekly (preferably on Wednesday/Thursday) during the Double-blind Treatment Period. The Structured Safety Evaluation is performed by study staff using a list of specific signs/symptoms (eg, mental status change, falls, gait disturbance).

6.1.2 Open-label Extension Phase

Patients who received at least 30 doses of study drug (either placebo or active) during the 12-week Double-blind Treatment Period and continue to meet other eligibility criteria will be eligible to receive open-label CR845 for an additional 52 weeks. The Open-label Extension Phase will be comprised of the Open-label Treatment Period and the Follow-up Period. The first visit and first dosing for the Open-label Extension Phase of the study will occur immediately on the day of the last visit of the Double-blind Treatment Period or up to 1 week following the Double-blind Treatment Period. Each patient will receive CR845 at a dose of 0.5 mcg/kg after each dialysis session, 3 times per week for up to 52 weeks, whether they had been previously administered placebo or CR845. Prescription dry body weight will be recorded at the start of and every 12 weeks during the Open-label Extension Phase; if there is a ±10% or more change from the prescription dry body weight recorded at Screening, then the CR845 dose will be adjusted according to the newly recorded dry body weight.

Patients will complete the 5-D Itch Scale during Weeks 4, 8, 12, 24, 36, and 52 (preferably at the end of the specified weeks).

Clinical laboratory tests, vital signs, adverse events, and concomitant medications will be monitored throughout the Open-label Treatment Period. Blood samples for inflammatory biomarkers will be collected periodically until the End-of-Treatment or Early Termination Visit. An electrocardiogram will be performed at the End-of-Treatment or Early Termination Visit.

The number and reason(s) for missed dialysis and the use of antipruritic medications will be recorded throughout the Open-label Extension Phase.

The last dose of open-label study drug will be administered at the last dialysis visit in Week 52.

6.1.3 Follow-up Period

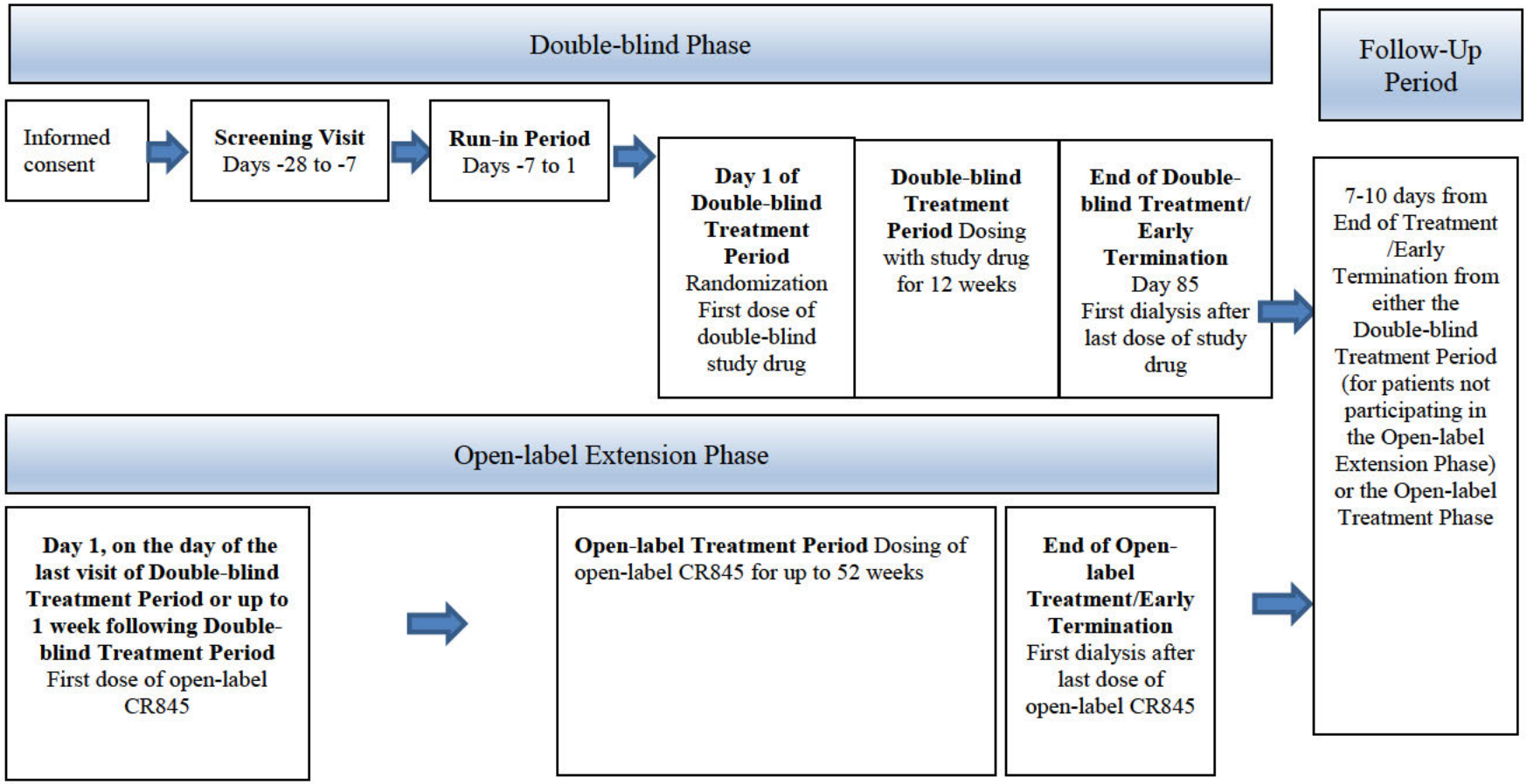
A final safety Follow-up Visit will be conducted 7-10 days after the End-of-Treatment Visit of the Double-blind Treatment Period for patients not participating in the Open-label Extension Phase, after the End-of-Treatment Visit of the Open-label Extension

Phase, or after the Early Termination Visit during either the Double-blind Treatment Period or the Open-label Extension Phase.

Vital signs, adverse events, and concomitant medications will be monitored during the Follow-up Period.

The study schematic is shown in Figure 1.

Figure 1. **CR845-CLIN3103 Study Schematic**



6.2 Selection of Study Population

Patients with ESRD receiving hemodialysis 3 times a week and experiencing moderate-to-severe pruritus will be considered for participation in this study.

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

Patients providing informed consent will be screened for inclusion in the study. All eligibility criteria must be met before a patient is randomized.

Rescreening will be considered on an individual patient basis and must first be approved by the Sponsor or designee. However, rescreening will not be permitted if a patient missed the entry criteria for itch intensity, ie mean NRS score < 5. A patient can only be rescreened once. Rescreening can only occur after at least two weeks from screening.

6.2.1 Inclusion Criteria

To be eligible for inclusion into the Double-blind Phase of the study, a patient must meet the following criteria:

1. Willing and able to provide written informed consent prior to participating in this study;
2. Able to communicate clearly with the Investigator and staff, able to understand the study procedures, and able and willing to comply with the study requirements, including providing written responses to questionnaires;
3. Male or female between 18 and 85 years of age, inclusive;
   Note: Subjects in Korea must be male or female between 19 and 85 years of age, inclusive;
4. Has ESRD and has 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 or electrolyte excesses may be enrolled as long as it is anticipated that no more than 1 such treatment will be required in any given week and no more than 4 occasions during the 12-week double-blind period. Patients routinely on 4 dialyses a week will not be eligible.
   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.
   Note 3: Patients receiving alternate dialysis modalities such as nocturnal dialysis will not be eligible.
5. If female, is not pregnant or nursing during any period of the study;

6. If female:
    a. Is surgically sterile; or
    b. Has been amenorrhoeic for at least 1 year and is over the age of 55 years; or
    c. Has a negative serum pregnancy test at screening and agrees to use acceptable contraceptive measures (eg, hormonal contraceptives, barrier with spermicide, intrauterine device, vasectomized partner, or abstinence) from the time of informed consent until 7 days after the last dose of study drug;
7. If male, agrees not to donate sperm after the first dose of study drug until 7 days after the last dose of study drug, and agrees to use a condom with spermicide or abstain from heterosexual intercourse during the study until 7 days after the last dose of study drug. (Note: No restrictions are required for a vasectomized male provided his vasectomy was performed ≥4 months prior to screening);
8. Has a prescription dry body weight between 40.0 and 135.0 kg, inclusive;
9. Has 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;
10. Prior to randomization:
    a. Has completed at least four out of eight Worst Itching Intensity Numeral Rating Scale (NRS) worksheets from the start of the 7-day Run-in Period up to and including the pre-randomization assessment on Day 1;
    b. Has a mean baseline Worst Itching Intensity NRS score ≥5, defined as the average of all non-missing scores reported from the start of the 7-day Run-in Period up to and including the pre-randomization assessment on Day 1.

To be eligible for inclusion into the Open-label Extension Phase of the study, each patient will have to fulfill the additional following criteria at the time of entry into the Open-label Extension Phase:

11. Has received at least 30 doses of the planned 36 doses of study drug during the Double-blind Phase of this study;
12. Has a prescription dry body weight ≥40 kg;
13. Continues to meet inclusion criteria 1 through 7.

6.2.2 Exclusion Criteria

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

1. Known noncompliance with dialysis treatment that in the opinion of the Investigator would impede completion or validity of the study;
2. Scheduled 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. Has a concomitant disease or a history of any medical condition that, in the opinion of the Investigator, could pose undue risk to the patient, impede completion of the study procedures, or would compromise the validity of the study measurements, including, but not limited to:
    a. Known or suspected history of alcohol, narcotic, or other drug abuse, or substance dependence within 12 months prior to screening;
    b. Significant systolic or diastolic heart failure (eg, New York Heart Association Class IV congestive heart failure [Appendix 1, Section 14.1]);
    c. Severe mental illness or cognitive impairment (eg, dementia);
    d. Any other relevant acute or chronic medical or neuropsychiatric condition within 3 months prior to screening (eg, diagnosis of encephalopathy, coma, delirium);
5. New or change of treatment received for itch including antihistamines and corticosteroids (oral, IV, or topical) within 14 days prior to screening;
6. New or change of prescription for opioids, gabapentin, or pregabalin within 14 days prior to screening;
7. Received another investigational drug within 30 days prior to the start of screening or is planning to participate in another clinical study while enrolled in this study;
8. In the opinion of the Investigator has pruritus attributed to a cause other than ESRD or its complications (eg, patients with concomitant pruritic dermatological disease or cholestatic liver disease) (Note: Patients whose pruritus is attributed to ESRD complications, such as hyperparathyroidism, hyperphosphatemia, anemia, or the dialysis procedure or prescription may be enrolled);
9. Has localized itch restricted to the palms of the hands;
10. Has pruritus only during the dialysis session (by patient report);
11. Is receiving ongoing ultraviolet B and anticipates receiving such treatment during the study;
12. Participated in a previous clinical study with CR845.

A patient will be excluded from the Open-label Extension Phase of the study if any of the additional following criteria are met at the time of entry into the Open-label Extension Phase:

13. Completed the Double-blind Phase of this study but exhibited adverse events during the course of the Treatment Period that may preclude continued exposure to the study drug;
14. Was noncompliant with protocol procedures during the Double-blind Phase of this study which is indicative of an inability to follow protocol procedures;
15. Has developed a concomitant disease or any medical condition that, in the opinion of the Investigator, could pose undue risk to the patient, impede completion of the study procedures, or would compromise the validity of the study measurements.

6.3 Removal of Patients from Therapy or Assessment

6.3.1 Discontinuation of Individual Patients

A patient may withdraw from the study at any time at his/her own request for any reason without prejudice to future medical care by the physician or at the institution.

A patient may be withdrawn at any time due to the following reasons:

1. At the discretion of the Investigator or the Sponsor for safety, behavioral, compliance, or administrative reasons, including, but not limited to:
    a. Lost to follow-up;
    b. Adverse event;
    c. Lack of therapeutic efficacy;
    d. Pregnancy;
    e. Eligibility (Inclusion/exclusion criteria);
    f. Subject non-compliance;
    g. Subject withdrew consent.
2. If a patient misses 3 consecutive doses either on Week 11 or Week 12 of the Double-blind Treatment Period (these patients may still be eligible for the Open-label Extension Phase at the discretion of the Investigator in consultation with the Sponsor).
3. If patient misses 6 consecutive doses at any time during the Double-blind Treatment Period (these patients may still be eligible for the Open-label Extension Phase at the discretion of the Investigator in consultation with the Sponsor).
4. At the discretion of the Sponsor/Medical Monitor, if a patient receives a prohibited concomitant medication according to Table 1.

5. Any patient who becomes pregnant during treatment must be withdrawn from the study (see Section 6.5.4.7).

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

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

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

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

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

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

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

6.3.2 Discontinuation or Suspension of Entire Study

The Sponsor may suspend or terminate the study or part of the study at any time for any reason. Reasons may include the following, among others:

1. Investigators have not been able to enroll patients within a reasonable period of time or according to inclusion/exclusion criteria;

2. The target number of subjects required for the study is enrolled earlier than expected;

3. Unexpected safety concern.

If the study is suspended or terminated, the Sponsor will ensure that applicable regulatory agencies and Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) are notified, as appropriate.

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

6.4 Treatments

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

6.4.1 Treatments Administered

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

Patients will receive IV CR845 at a dose of 0.5 mcg/kg or placebo after each dialysis session, generally 3 times per week for up to 64 weeks (ie, 12 weeks double-blind and 52 weeks open-label) as an IV bolus into the venous line of the dialysis circuit at the end of each dialysis session and may be given either during or after rinse back of the dialysis circuit. If the dose is given after rinse back, following the IV push of study drug the venous line must be flushed with at least 10 mL of normal saline. If the dose is given during rinse back, no additional normal saline is needed to flush the line. If a patient receives additional dialysis during a given week for any reason, an additional dose of CR845 or placebo will be administered following dialysis. A maximum of 4 doses per week is allowed. No additional doses will be given for patients receiving an additional unscheduled ultrafiltration treatment.

The patient's prescription dry body weight (ie, 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 Double-blind Treatment Period.

During the Open-label Extension Phase, the patient's current prescription target dry body weight should be compared to the screening dry body weight. If the difference is less than ±10%, then continue dosing based on the patient's dry body weight recorded at screening. If the difference is ±10% or more, use the patient's newly recorded dry body weight to calculate the volume of CR845 to be administered. Dosing will be adjusted every 12-weeks if prescription dry body weight changes by ±10% or more from dry body weight recorded at screening.

6.4.2 Identity of Investigational Product(s)

6.4.2.1 Formulation of Study Drug

Study drug will be supplied by the Sponsor as a solution in 2-mL glass vials containing a minimum extractable volume of 1.3 mL of CR845 at a concentration of 0.05 mg/mL in

0.04 M isotonic acetate buffer, pH 4.5. The composition of the CR845 solution is 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 a minimum 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 placebo 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.

6.4.2.2 Packaging, Labeling, and Storage Stability of Study Drug

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

For the Double-blind Treatment Period vials will be packaged (blinded) in boxed kits (also blinded) containing 40 vials per box (4 extra vials for backup). Kits will be labeled with patient ID number and kit number. A single box of vials will be assigned to a patient.

For the Open-label Extension Phase, vials will be packaged in boxed kits containing 12 vials per box. Kits will be labeled with patient ID number and kit number. A single box of vials will be assigned to a patient.

Labeling of the vials and kits will conform to the regulations required by each country.

6.4.2.3 Individual Dose Labeling

One syringe will be prepared for each patient on each dosing day. Syringes and syringe labels will be provided. Refer to the ISF for details.

6.4.3 Drug Accountability

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

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

6.4.4 Method of Assigning Patients to Treatment Groups

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). Patients will be randomized in a 1:1 ratio to receive either CR845

0.5 mcg/kg IV or matching placebo IV during the Double-blind Treatment Period. Patients will be stratified into 2 strata according to their use or non-use of concomitant medications to treat their itch during the pre-randomization week (Run-in Period) as well as the presence or absence of specific medical conditions. These specific medical conditions include:

- History of fall or fracture (related to fall)
- Confusional state or mental status change or altered mental status or disorientation
- Gait disturbance or movement disorder

All eligible patients will receive CR845 at a dose of 0.5 mcg/kg starting on Day 1 of the Open-label Extension Phase.

6.4.5 Preparation of CR845

In the Double-blind Phase of the study, a single vial of study drug will be used for each patient. Each patient's prescription dry body weight will not exceed 135.0 kg.

In the Open-label Extension Phase of the study, 1 vial of CR845 will be used for patients with a prescription dry body weight ≤135.0 kg. For patients with a prescription dry body weight >135.0 kg, 2 vials of CR845 will be used to ensure that the full volume of study drug can be prepared. Further details will be provided in the ISF.

Information on the study drug preparation can be found in the Pharmacy Manual.

6.4.6 Management of Missed Doses

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

Contact the Medical Monitor if patient compliance or safety is of concern.

6.4.7 Treatment Compliance

Patient compliance with study drug is documented as part of standard procedures at the dialysis units where study drug is administered.

6.4.8 Blinding

During the Double-blind Treatment Period, patients, Investigators, study staff, and the Sponsor will be blinded to study drug assignment.

For medically urgent or emergent situations that necessitate knowledge of study drug assignment for patient management, the blind may be broken via the IVRS/IWRS. Except for when patient's care requires the treatment assignment immediately, the Medical Monitor should be contacted prior to breaking the blind. The Sponsor and Medical Monitor will receive a report whenever a patient blind is broken.

6.4.9 Prior, Concomitant, and Prohibited Medications

6.4.9.1 Prior and Concomitant Medications

Prior medications (including vitamins and herbal supplements) are defined as those that the patient has taken any time during the 3 months prior to the first dose of study drug on Day 1 of the Double-blind Treatment Period. Concomitant medications are medications that are taken from after the start of the first dose of study drug on Day 1 of the Double-blind Treatment Period through the end of the Follow-up Period.

Use of antipruritic medications during the study will be recorded on an ongoing basis, starting at screening. Patients having a prescription PRN for the use of anti-itch medication will be stratified as using anti-itch medication even if such medications were not reported to be used during the Run-In period. Medications known for potential anti-pruritic effects but used for a different indication (ex. use of gabapentin for pain management) will not be reported as anti-pruritic medications.

All prior and concomitant medications, including over-the-counter medications used by patients during this study, are to be recorded in the appropriate page of the eCRF, as applicable.

6.4.9.2 Restricted and Prohibited Medications

During the Treatment Period for either the Double-blind Phase or Open-label Extension Phase, the following medications will be restricted or prohibited (Table 1).

Table 1. Restricted and Prohibited Medications

Drug, Drug Class, or Treatment	Restrictions During the Treatment Period
Investigational drug (other than the study drug)	**Not allowed**
Ultraviolet B treatments	**Not allowed**
Naloxone, naltrexone, or mixed agonist-antagonists (eg, buprenorphine and nalbuphine)	**Not allowed** from the start of dosing of the Double-blind Treatment Period to the end of the Open-label Treatment Period, unless needed to treat an adverse event or emergent medical condition acutely.
Antihistamines (oral, IV, or topical) Corticosteroids (oral, IV, or topical) treatments Opioids Gabapentin, pregabalin	**Changes to current prescription should be avoided** from screening to the end of the Double-blind Treatment Period unless for the acute treatment of an adverse event or emergent medical condition (in this case, notify the study medical monitor and, as appropriate, report adverse events). No new medication to treat itch should be initiated during the Double-blind Treatment Period.

All new concomitant medications or change of frequency and doses of a concomitant medication will be recorded.

6.5 Study Assessments and Procedures

6.5.1 Schedule of Events for the Double-blind Phase

Study procedures for the Double-blind Treatment Period are summarized in Table 2.

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

Table 2. Schedule of Events: Double-blind Phase

Study Procedures	Screening Period		Double-blind Treatment Period[a]						Double-blind End of Treatment[b]/ Early Termination	Follow-Up Period (for patients not participating in Open-label Extension Phase ONLY)
	Screening Visit	Run-in Period	Week 1			Weeks 2 to 12			Week 13	
Visit Days →	Day -28 to Day -7	Day -7 to Day 1	M/Tu	W/Th	F/Sa	M/Tu	W/Th	F/Sa		FU Days 1[b]-10
	-28 to -7	-7 to 1	1	3	5	8	10	12	85	85 to 95
						15	17	19		
						22	24	26		
						29[k]	31	33		
						36	38	40		
						43	45	47		
						50	52	54		
						57[k]	59	61		
						64	66	68		
						71[k]	73	75		
						78	80	82		
Administrative procedures										
Informed consent	X									
Inclusion/exclusion criteria	X		X[c]							
Medical history/Prior Medications (including antipruritic medications)/Demographics	X	X[c]	X[c]							
Randomization			X							
Safety and efficacy evaluations										
Physical examination	X									
Prescription dry body weight	X									
Pre-dialysis 12-lead electrocardiogram	X[d]								X[d]	
Pre-dialysis vital signs	X		X[e]			X[e]			X[e]	X[f]
Hematology, serum chemistry (pre-dialysis)[g]	X		X						X	
Serum pregnancy (females of childbearing potential only)	X[o]								X	

Table 2. Schedule of Events: Double-blind Phase (Continued)

Study Procedures	Screening Period		Double-blind Treatment Period[a]						Double-blind End of Treatment[b]/ Early Termination	Follow-Up Period (for patients not participating in Open-label Extension Phase ONLY)
	Screening Visit	Run-in Period	Week 1			Weeks 2 to 12				
Visit Days →	Day -28 to Day -7	Day -7 to Day 1	M/Tu	W/Th	F/Sa	M/Tu	W/Th	F/Sa	First Day of Week 13	FU Days 1[b] -10
	-28 to -7	-7 to 1	1	3	5	8	10	12	85	85 to 95
						15	17	19		
						22	24	26		
						29[k]	31	33		
						36	38	40		
						43	45	47		
						50	52	54		
						57[k]	59	61		
						64	66	68		
						71[k]	73	75		
						78	80	82		
Safety and efficacy evaluations										
Patient training on PRO worksheets	X[h,i]	X[i]	X						X	
Worst Itching Intensity NRS (daily)[j]		X	Record on an ongoing basis						X	
Skindex-10 Scale, 5-D Itch Scale[k]			X			X[k]			X[k]	
Patient Global Impression of Change									X	
Record number of missed dialysis visits and reason(s)			Record on an ongoing basis							
IV administration of study drug			Record on an ongoing basis							
Inflammatory biomarker samples[l]			X						X	
Adverse event monitoring	X	X	Record on an ongoing basis						X	X
Concomitant medications (including antipruritic medications)[m]			X	Record on an ongoing basis					X	X
Structured Safety Evaluation[n]		X		X			X			

EoT = End of Treatment; ET = Early Termination; F = Friday; FU = follow-up; IV = intravenous; M = Monday; NRS = numerical rating scale; PRO = patient-reported outcome; Sa = Saturday; Th = Thursday; Tu = Tuesday; W = Wednesday

a. Each visit during the Double-blind Treatment Period will coincide with the patient's normal dialysis treatments.
b. The End-of-Treatment Visit in the Double-blind Phase will be the first dialysis visit following the last dose of study drug (ie, first dialysis on Week 13 [Day 85]), which also corresponds to Day 1 of the Follow-up Period (FU Day 1). Only patients not participating in the Open-label Extension Phase are required to complete the Follow-up Period.
c. 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. Antipruritic medication will be updated at each dialysis visit during the Run-in Period.
d Electrocardiograms must be performed prior to the start of dialysis at Screening, Day 85 (End of Treatment), or at Early Termination visit.
e Pre-dialysis vital signs, including body temperature, heart rate, and blood pressure, will be recorded on Days 1, 15, 29, 43, 57, 71 and 85 (End of Treatment), or at Early Termination visit only when the patient is in a sitting or semi-recumbent position. Heart rate will be measured at each dialysis; if heart rate is clinically significant and outside the prespecified visits per the Schedule of Events, the heart rate will be recorded on the relevant CRF page.
f Pre-dialysis vital signs, including body temperature, heart rate, and blood pressure, will be recorded at the Follow-up Visit (7-10 days after EoT/ET visit). Heart rate will be measured at each dialysis.
g. Blood samples for clinical laboratory evaluation will be taken at Screening, and on Days 1 and 85 (End of Treatment), or at Early Termination visit only.
h. Training on Worst Itching Intensity NRS will be conducted prior to the first day of the Run-in Period (Day -7).
i. Training on Skindex-10 Scale and 5-D Itch Scale may be performed at any time during Screening prior to randomization on Day 1 of the Double-blind Treatment Period.
j. Patients will be requested to complete their Worst Itching Intensity NRS worksheets each day at a similar time (either at home on non-dialysis days around the normal start time of their dialysis or in the dialysis unit). On dialysis days, the worksheets will be completed prior to or during dialysis, but must be completed prior to dosing.
k. 5-D Itch Scale and Skindex-10 Scale completed on Day 1 and the first visit of Weeks 5, 9 and 11 (on Days 29, 57 and 71) and Week 13 (Day 85). The 5-D Itch Scale will preferably be completed first. If the first visit of the week is missed, the patient may complete the worksheets at their next visit for the same week. The worksheets will be completed prior to or during dialysis (preferably within 1 hour of the dialysis), but must be completed prior to dosing.
l. Biomarker samples must be collected prior to the start of dialysis on Day 1 and Day 85.
m. Concomitant medications including antipruritic medication will be updated at each dialysis visit during the Double-blind Treatment Period, and until the end of the Follow-up Period.
n. A list of specific signs/symptoms will be verified with the patient by qualified site staff, preferably to be completed on Wednesday/Thursday each week during the Run-in Period, the Double-blind Treatment Period and the Follow-up Period. It is not to be completed on Monday/Tuesday.
o. The serum pregnancy test must be performed within 7 days prior to the first study dose.

6.5.2 Schedule of Events for the Open-label Extension Phase

Study procedures for the Open-label Extension Phase are summarized in Table 3.

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

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

Table 3. Schedule of Events: Open-label Extension Phase

Study Procedures	Open-label Treatment Period[a] Up to 52 Weeks of Dosing							Follow-Up Period
	Day 1[c]	Week 4[a]	Week 8[a]	Week 12[a]	Week 24[a]	Week 36[a]	First Dialysis of Week 53[b] End of Treatment /Early Termination	7 - 10 days after End of Treatment/Early Termination
Administrative procedures								
Inclusion/exclusion criteria	X[d]							
Safety and other evaluations								
Physical examination	X							
Record prescription dry body weight[e]	X[e]	Record every 12 weeks[e]						
Pre-dialysis 12-lead electrocardiogram[f]							X	
Pre-dialysis vital signs[g]	X	X	X	X	X	X	X	X
Hematology, serum chemistry (pre-dialysis)				X	X		X	
Serum pregnancy test for women of childbearing potential only				X	X		X	
Record number of missed dialysis visits and reason(s), as applicable		Record on an ongoing basis						
IV administration of study drug	X[h]	Dose after each dialysis up to Week 52 included[h]						

Table 3. Schedule of Events: Open-label Extension Phase

(Continued)

Study Procedures	Open-label Treatment Period[a] Up to 52 Weeks of Dosing							Follow-Up Period
	Day 1[c]	Week 4[a]	Week 8[a]	Week 12[a]	Week 24[a]	Week 36[a]	First Dialysis of Week 53[b] End of Treatment /Early Termination	7 - 10 days after End of Treatment/Early Termination
Safety and other evaluations								
5-D itch scale[i]		X	X	X	X	X	X	
Inflammatory biomarker samples[j]					X		X	
Adverse event monitoring	Record on an ongoing basis[k] →							
Concomitant medications (including antipruritic medications)	Record on an ongoing basis[k] →							

IV = intravenous

a. Each visit during the Open-label Treatment Period will coincide with the patient's normal dialysis treatments. The study visit may occur on any chosen dialysis day of a scheduled week as long as all assessments are completed during that visit. However, it is recommended to avoid the first dialysis day of the week. Patients who miss one of the scheduled study visit weeks (eg, Week 4) may complete the visit procedures for this visit at their next dialysis treatment as long as it is within 2 weeks of the originally scheduled visit date.

b. The End-of-Treatment Visit will be the first dialysis visit following the last dose of study drug (ie, first dialysis on Week 53).

c. Day 1 of the Open-label Extension Phase can occur immediately on the day of the last visit of the Double-blind Treatment Period or up to 1 week following the Double-blind Treatment Period.

d. Prior to dosing on Day 1 of the Open-label Extension Phase, the inclusion/exclusion criteria will be confirmed.

e. The prescription dry body weight will be captured from the dialysis prescription and will be recorded on Day 1 and every 12 weeks during the Open-label Treatment Period (during Weeks 12, 24, 36, and 48). If there is a ±10% or more change in prescription dry body weight compared to the dry body weight recorded at screening, then the CR845 dose will be adjusted according to the newly recorded dry body weight. The date of prescription dry body weight change will also be recorded.

f. Electrocardiogram must be performed prior to the start of dialysis.

g. Vital signs, including body temperature, heart rate, and blood pressure, will be obtained at the specified visits while the patient is in a sitting or semi-recumbent position prior to the start of dialysis. Heart rate will be measured at each dialysis; if the heart rate is clinically significant and outside the prespecified visits per the Schedule of Events the heart rate will be recorded on the relevant CRF page.

h. Administered after each dialysis as an IV bolus.

i. To be completed in the dialysis unit at any time prior to or during dialysis, but must be done prior to dosing. Preferably at the end of the specified week, which corresponds to the beginning of the following calendar week (ie, end of Week 4 is the Monday/Tuesday of Week 5).
j. Biomarker samples must be collected prior to the start of dialysis.
k. Adverse events and concomitant medications will be recorded starting on Day 1 of the Open-label Extension Phase.

6.5.3 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
- 5-D Itch Scale
- Patient Global Impression of Change

Patients will be trained on completion of the Worst Itching Intensity NRS scale prior to the first visit of the Run-in Period, and will be trained on the other itch-related PRO measures at any time prior to Day 1 of the Double-blind Treatment Period. All questionnaires must be completed in strict adherence to the Training Manual for Patient Reported Assessments.

6.5.3.1 Worst Itching Intensity Numerical Rating Scale

Intensity of itch will be measured using an NRS scale (Appendix 2, Section 14.2) on a worksheet on 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 nondialysis days.

The Worst Itching Intensity NRS has been widely utilized for evaluation of chronic itch, including uremic pruritus [Kumagai 2010; Pisoni 2006; Mathur 2010; Ständer 2013].

6.5.3.2 Skindex-10 Scale

Developed specifically for uremic pruritus, the Skindex-10 Scale (Appendix 3, Section 14.3) is an instrument for measurement of quality-of-life that correlates with itch intensity [Mathur 2010]. Patients are asked to mark 1 of 7 boxes numbered from 0 (labeled with the anchor phrase "never bothered") to 6 (labeled as "always bothered") for each of the 10 questions describing how often they have been bothered by their itch and its impact over the past week. 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).

6.5.3.3 5-D Itch Scale

The 5-D Itch Scale was developed as a brief, multidimensional questionnaire designed to be useful as an outcome measure in clinical studies. The 5 dimensions of itch assessed are degree, duration, direction, disability, and distribution (Appendix 4, Section 14.4).

Patients are asked to mark boxes that best describe the impact of their itch over the past 2 weeks. The scale has been validated in patients with chronic pruritus, including hemodialysis patients and has been shown to be sensitive to changes in pruritus over time [Elman 2010].

6.5.3.4 Patient Global Impression of Change

The Patient Global Impression of Change is a global PRO measure that assesses the change in itch (no change, improvement or worsening) overall relative to the start of the study [Dworkin 2005]. The scale has only 1 item, and the patient is asked to mark the category that best describes the change in itch ranging from "Very Much Improved" to "Very Much Worse" (Appendix 5, Section 14.5).

6.5.4 Safety Assessments

During both the Double-blind and Open-label Extension Phases, the safety assessments for each patient are the following:

- Severity, seriousness, and relationship of adverse events to study drug
- Structured Safety Evaluation by site staff (Double-blind Phase only)
- Physical examination
- Vital signs
- 12-lead ECGs
- Clinical laboratory tests

6.5.4.1 Adverse Events

Definition of Adverse Events

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

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

- Any new sign, symptom, or disease;
- Any new clinically significant or symptomatic laboratory/diagnostic test abnormality;
- Any clinically significant worsening of laboratory/diagnostic test abnormality;

- Any worsening (ie, clinically significant change in frequency, nature, and/or intensity) of a pre-existing condition.

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

Signs and symptoms will be reported individually as adverse events (non-serious), unless a medical diagnosis was provided. Medical diagnosis, whenever provided, will be reported rather than individual signs and symptoms.

Any adverse event that satisfies any of the seriousness criteria described below will be reported as an SAE using the SAE Report Form, in addition to documenting in the eCRF. Serious adverse events that occurred up to 30 days after the last dose of study drug need to be documented on an SAE Report Form if they are deemed by the Investigator to be "Related" to study drug.

An SAE that occurred after a period of 30 days from the last dose of study drug must be reported when the investigator becomes aware of it and if there is a possible relationship to the study drug or the conduct of the study.

Adverse Event Severity Assessment

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

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

Definition of Serious Adverse Events

An SAE is any untoward medical occurrence that:

- Results in death;
- Is life-threatening;

  NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does

not refer to an event which hypothetically might have caused death if it were more severe.

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

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

Severe versus Serious Adverse Event

The term "severe" is used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). An adverse event as well as an SAE must be assessed for severity. An adverse event that is assessed as severe should not be confused with an SAE. "Severity" is not the same as "Serious," which is based on patient outcome or reaction criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Adverse Event Causality or Relatedness to the Study Drug

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

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

Adverse Event Documentation and Follow-up

All adverse events, including observed, elicited, or volunteered problems, complaints, or symptoms are to be recorded on the adverse event page in the patient's eCRF from the

time the patient signs the ICF and until the Follow-up Visit/early termination, whether or not judged by the Investigator to be related to study drug. The need to capture this information is not dependent upon whether adverse events are related to study drug. Serious adverse events that occurred up to 30 days after the last dose of study drug need to be documented on an SAE Report Form if they are deemed by the Investigator to be "Related" to study drug.

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

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

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

It is anticipated that some patients may undergo procedures and/or experience events that are common in the study population under investigation, independent of study therapy. Preplanned procedures and procedures (eg, kidney transplant, catheter replacement) or events that are independent of study therapy, according to the Investigator's assessment, will be documented as specified in the Safety Management Plan.

Serious Adverse Event Notification, Documentation, and Reporting

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

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

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

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

The Sponsor will comply with the applicable local regulatory requirements related to reporting of SAEs to the appropriate regulatory authorities in the countries and regions this study is conducted, while the Investigator and designated study personnel will comply with the applicable local regulatory requirements related to reporting of SAEs to the IRB/IEC and the Sponsor.

It is the responsibility of the Sponsor or designee to send all regulatory reports to the appropriate regulatory authorities. Adverse events that are serious, related to the study drug, and unexpected (per the Investigator's Brochure) will be reported to the regulatory authorities as specified in the Safety Management Plan.

For regulatory reporting purposes, the Sponsor can upgrade the Investigator's assessment (eg, from not related to related); however, Sponsor 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 study drug and the event, then the relationship should be considered to be related to study drug.

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

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

6.5.4.2 Structured Safety Evaluation

A weekly Structured Safety Evaluation will also be used during the Double-Blind Phase to proactively identify and monitor adverse events of special interest.

The Structured Safety Evaluation will be performed once during the Run-in Period and weekly (preferably on Wednesday/Thursday) during the Double-blind Treatment Period. The Structured Safety Evaluation will be performed by qualified study staff using a list of specific signs/symptoms, including mental status change, falls and gait disturbance.

6.5.4.3 Physical Examination

Physical examinations will include an examination of the heart, lungs, abdomen, extremities, and neurological and vascular systems. Clinically significant abnormalities or worsening findings observed after the first dose of study drug will be reported as treatment-emergent adverse events (TEAEs).

6.5.4.4 Vital Signs

Vital signs include sitting or semi-recumbent body temperature, heart rate, and blood pressure and will be measured prior to start of dialysis.

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

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

Heart rate will be collected at each dialysis; if clinically significant and outside the prespecified visits per schedule of events, the heart rate will be recorded on the relevant CRF page.

6.5.4.5 Electrocardiogram

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

6.5.4.6 Clinical Laboratory Tests

Blood samples for clinical laboratory tests including hematology, serum chemistry, and serum pregnancy will be taken prior to dialysis and will be analyzed by a central laboratory. The laboratory tests include the following:

Assessment	**Parameters to be analysed**
Serum Chemistry	Albumin, Alkaline Phosphatase, ALT/SGPT, AST/SGOT, Bilirubin (Total), BUN, Calcium, Chloride, Creatinine, Glucose, Phosphorus, Potassium, Sodium
Hematology	Basophil %, Basophil (Absolute), Eosinophil %, Eosinophil (Absolute), Hematocrit, Hemoglobin, Lymphocyte %, Lymphocyte (Absolute), MCH, MCHC, MCV, Monocyte %, Monocyte (Absolute), Neutrophil %, Neutrophil (Absolute), Platelet, RDW, Red Blood Cells, White Blood Cells
Serum Pregnancy (females of childbearing potential only)	Human chorionic gonadotropin (HCG)

Processing and shipment of central laboratory samples will be described in the Laboratory Manual.

6.5.4.7 Contraception and Pregnancy

All females of childbearing potential will have blood samples taken at Screening for serum pregnancy testing. Females are considered to be of childbearing potential unless they are:

- Surgically sterile (ie, 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

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

Medically acceptable methods of birth control include hormonal contraceptives for at least 1 cycle of treatment before study enrollment, an intrauterine device, and barrier with spermicide.

Per inclusion criteria, male patients will agree not to donate sperm after the first dose of study drug until 7 days after the last dose of study drug, and will agree to use a condom with spermicide or abstain from heterosexual intercourse during the study until 7 days after the last dose of study drug. No restrictions are required for a vasectomized male, provided his vasectomy was performed ≥4 months prior to dosing. If sexual abstinence is chosen by the patient, it must be the preferred and usual lifestyle of the patient and must be practiced for the entire duration of the study.

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

If a patient becomes pregnant during the Double-blind Treatment Period or Open-label Extension Phase or within 7-10 days after the last dose of study drug, the Investigator will immediately discontinue the patient from the study and contact the Sponsor or designee. Diligent efforts will be made to determine the outcome for all pregnancies in the clinical study. Information on the status of the mother and the child will be forwarded to the Sponsor. Generally, follow-up will occur within 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported. Both maternal and paternal exposure will be collected. For exposure involving the female partner of a male patient, the necessary information must be collected from the patient while respecting the confidentiality of the partner. A pregnancy report will be completed.

6.5.5 Additional Assessments

The following additional assessments will be collected during the Double-blind and Open-label Extension Phases:

- Inflammatory biomarkers
- Missed dialysis visits

6.5.5.1 Inflammatory Biomarkers

Inflammatory biomarkers, such as interleukin (IL)-6, IL-8, and granulocyte macrophage-colony stimulating factor will be measured, as defined in the statistical analysis plan (SAP). A blood sample of sufficient volume to provide for replicate assays of each biomarker will be collected prior to dialysis per the schedules of events.

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

6.5.5.2 Missed Dialysis Visits

The number and reason(s) for missed dialysis will be recorded.

7.0 Discussion and Justification of Study Design

7.1 Discussion of Study Design and Choice of Control Groups

The double-blind part of the study was designed to evaluate the efficacy and safety of IV CR845 in hemodialysis patients with moderate-to-severe pruritus. A randomized, double-blind design was chosen to minimize bias. A 12-week duration of treatment was selected to demonstrate durability of the efficacy observed in a prior 8-week treatment study (ie, Study CR845-CLIN2101) and to further evaluate safety during a longer exposure. The primary efficacy endpoint was determined using the Worst Itching Intensity NRS scale, which measures itching intensity over 24 hours. This scale has been validated for this patient population and is identical to the primary efficacy endpoint used in the dose-ranging, Phase 2 study, CR845-CLIN2101.

The open-label part of the study was designed to evaluate the long-term safety of CR845 0.5 mcg/kg IV administered after each dialysis session (generally 3 times per week for up to 52 weeks) in patients who completed the 12-week Double-blind Treatment Period of this study. This design is commonly used in clinical development to obtain long-term safety information. The duration of the study is in accordance with International Council for Harmonisation (ICH) and FDA guidance [Guidance for Industry February 2016].

7.2 Selection of Doses in the Study

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

7.3 Appropriateness of Measurements

Standard clinical, laboratory, and statistical procedures and methodology will be utilized in this study. The PRO assessments to be used in this study are appropriate.

8.0 Statistical Methods

8.1 General Considerations

This section describes the statistical analysis of efficacy and safety data collected during the Double-blind Phase only. The analysis of safety and efficacy data collected during the Open-label Extension Phase will be included in the SAP.

The SAP will provide a detailed description for the handling of missing data, patient eligibility criteria for the analysis, and statistical methodology. If differences occur between analyses of double-blind data described in the SAP and the current protocol, those found in the SAP will assume primacy. In addition, the SAP will provide details for the analysis of data collected during the Open-label Extension Phase, including the analysis of safety data during exposure to CR845 across both the Double-blind and the Open-label Extension Phases.

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.

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

8.2 Determination of Sample Size

The planned sample size for this study is 350 (175 per treatment group) male and female hemodialysis patients with chronic moderate-to-severe pruritus (mean baseline 24-hour Worst Itching Intensity NRS score ≥5), randomized at approximately 95 clinical sites. The sample size may be increased to 500 patients (250 per treatment group) based on the results of a planned unblinded interim assessment conducted when approximately 50% of the planned 350 first patients have been randomized and have either completed the 12-week Double-blind Treatment Period or have discontinued from double-blind treatment early. The planned interim assessment will be conducted by an Independent Data Monitoring Committee (IDMC). Details related to the sample size re-estimation are included in Section 8.4.1.

The sample size calculation is based on results of a completed Phase 2 double-blind, placebo-controlled study (CR845-CLIN2101) of CR845 in hemodialysis patients who had moderate-to-severe pruritus. In this study, approximately 30% of patients randomized to the placebo group reported ≥3-point improvement from baseline with respect to the 24-hour Worst Itching Intensity NRS at the end of treatment (Week 8). The proportion of patients who received CR845 and reported a similar improvement in itch scores ranged from approximately 60% to 45% (ie, 30% to 15% difference from

placebo), depending on the dose of active study drug (0.5 mcg/kg, 1.0 mcg/kg, 1.5 mcg/kg).

Given a sample size of 350 patients (175 per treatment group) and assuming a true response rate of 30% for the placebo group and a true response rate of 50% for the CR845 group (defining response as an improvement from baseline ≥3 points with respect to the Worst Itching Intensity NRS at Week 12), a 2-sided continuity corrected Chi-square will have 96% power to detect a treatment difference. The power of this test statistic would be ≥84% for differences from placebo as low as 0.16 (Table 4).

Table 4. Power as a Function of Effect Size (N = 175 per arm)

Placebo Response	0.30	0.30	0.30	0.30
CR845 Response	0.50	0.48	0.46	0.45
Odds Ratio	2.333	2.154	1.988	1.909
Power[a]	96%	92%	84%	79%

a. Power for a 2-sided Chi-square continuity-corrected test and a 5% Type 1 error.

Based on results of a planned interim assessment, the sample size may be increased up to 500 patients (250 per treatment group). Given this maximum sample size, and assuming a true response rate of 30% in the placebo group, a 2-sided continuity corrected Chi-square would have approximately 90% power to detect a treatment difference when the CR845 response rate is 45% (a 15% difference from placebo) (Table 5).

Table 5. Sample Size as a Function of Odds Ratio (90% Power)

Placebo Response	0.30	0.30	0.30	0.30	0.30
CR845 Response	0.50	0.48	0.46	0.45	0.44
Odds Ratio	2.333	2.154	1.988	1.909	1.833
Sample Size[a]	134	164	204	230	262

a. Sample size for a 2-sided Chi-square continuity-corrected test and a 5% Type 1 error.

8.3 Randomization

Before the start of the study, a computer-generated randomization schedule will be prepared. Randomization will be performed using an IVRS/IWRS. Patients will be randomized in a 1:1 ratio to receive either CR845 0.5 mcg/kg IV or matching placebo IV during the Double-blind Treatment Period. Patients will be stratified according to their use or non-use of concomitant medications to treat their itch during the week prior to randomization (Run-in Period) as well as the presence or absence of specific medical conditions. These medical conditions include:

- History of fall or fracture (related to fall)
- Confusional state or mental status change or altered mental status or disorientation
- Gait disturbance or movement disorder

All eligible patients will receive CR845 at a dose of 0.5 mcg/kg starting on Day 1 of the Open-label Extension Phase.

8.4 Interim Analysis

8.4.1 Sample Size Re-estimation

An unblinded interim analysis for sample size re-estimation will be conducted when approximately 50% of the first 350 patients have been randomized and have either completed the 12-week Double-blind Treatment Period or have discontinued from double-blind treatment early. The planned interim assessment will be conducted by an IDMC. An unblinded statistician who will not be part of the study team will provide results of the interim analysis to the IDMC members. Members of the IDMC will not participate in the Data Safety Monitoring Board (DSMB) and will not be members of the study team. During the interim assessment, the study team will remain blinded to the data; however, the IDMC will receive unblinded summary results to implement the decision rule for sample size re-estimation. The IDMC will only communicate the decision to either keep the original sample size or to increase it; no other results will be provided to blinded staff. The DSMB will be made aware of the decision, but not given the results that were the basis of the decision.

[redacted]

8.4.2 Safety Data Review

Safety data will be reviewed on an ongoing basis by the Sponsor and a DSMB. The operation of the DSMB will be governed by a charter that will describe the meeting frequency, procedures, and requirements for reporting its observations to the Sponsor.

8.5 Analysis Populations

The Enrolled Population is defined as the group of patients who sign informed consent.

The ITT Population is defined as the group of patients who are randomized to a treatment group.

The Double-blind Safety Population is defined as the group of randomized patients who received at least 1 dose of double-blind study drug during the Double-blind Treatment Period.

Following the intent-to-treat principle, patients in the ITT Population will be analyzed according to their randomized treatment, regardless of the actual treatment received. Patients in the Double-blind Safety Population will be analyzed according to the actual treatment received. The Double-blind Safety Population will be used to analyze all safety endpoints collected during the Double-blind Phase, while the ITT Population will be used to analyze all efficacy endpoints collected during the Double-blind Phase.

The Per-Protocol Population is defined as the subset of patients in the ITT Population who do not have any major protocol deviations that could affect the efficacy analyses of the double-blind data. An analysis of the primary and secondary efficacy variables for the Per-Protocol Population will be performed.

Key exclusions from the Per-Protocol population include patients who:

- Received less than 80% of the planned study drug doses
- Had a mean baseline Worst Itching Intensity score < 5.0
- Had a missing average 24-hour weekly Worst Itching NRS score for ≥25% of study weeks
- Had significant amounts of restricted and prohibited medications (Section 6.4.9) based on medical review
- Received a different treatment than the treatment to which they were randomized

Inclusion in the Per-Protocol Population will be determined prior to unblinding the data.

The Open-label Safety Population is defined as the group of patients who receive at least 1 dose of study drug in the Open-label Extension Phase. The Open-label Safety Population will be used to analyze all safety endpoints collected during the Open-label Extension Phase, and during exposure to CR845 combining data from both the Double-blind and the Open-label Extension Phases.

8.6 Statistical Summary and Analysis

8.6.1 Patient Disposition

For the Double-blind Phase, the number of patients enrolled, treated, completed, or discontinued from the study, along with the reason for discontinuation, will be summarized overall and by treatment group.

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

In addition, the number of patients in each analysis population will be tabulated.

8.6.2 Protocol Deviations

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

8.6.3 Demographic and Baseline Characteristics

Demographic and baseline patient characteristics will be summarized overall and by treatment group and will include age at screening, age category (<45, 45 to >65, 65 to <75, ≥75), gender, ethnicity, race, and prescription dry body weight (kg). Height will not be collected.

Baseline characteristics of the disease will also be summarized overall and by treatment group, and will include variables such as etiology of chronic kidney disease, years since ESRD, duration of pruritus, and time on chronic hemodialysis.

8.6.4 Medical History

Medical history data will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and summarized by MedDRA System Organ Class (SOC), Preferred Term, and treatment group. The data will also be listed, including the verbatim investigator description of the relevant medical condition, the coded terms (SOC, Preferred Term), start date, end date, and whether or not the condition is ongoing.

A separate coding listing will be created with all the distinct levels of SOC, Preferred Terms, and the verbatim investigator description reported in the study. Sorting will be alphabetically by SOC, Preferred Term, and then verbatim description.

8.6.5 Prior and Concomitant Medications

All medications will be coded using the World Health Organization Drug Dictionary. All prior and concomitant medications will be listed and summarized separately by Anatomical Therapeutic Chemical class 3 (ATC 3), Preferred Term, and treatment group. The use of medications will be summarized separately by study period. Additionally, a coding listing of unique medications and their corresponding coding will be presented.

8.6.6 Antipruritic Medication

Prior and concomitant antipruritic medications will be summarized separately by study period; summaries will be presented by ingredient rather than by ATC codes.

8.7 Efficacy Analysis

8.7.1 Primary Efficacy Endpoint

The primary efficacy endpoint is defined as the proportion of patients achieving ≥3-point improvement from baseline with respect to the weekly mean of the daily 24-hour Worst Itching Intensity NRS at Week 12 (Days 79 to 85) of the Double-blind Treatment Period.

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 scores reported during a specific week during the Double-blind Treatment Period (eg, Days 2 to 8, Days 9 to 15, Days 16 to 22, … Days 79 to 85) divided by the number of days with nonmissing 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 24-hour Worst Itching Intensity NRS scores collected over the Run-in Period, including pre-randomization assessments collected on Day 1.

In the primary efficacy analysis, missing NRS data will be imputed using a multiple imputation (MI) approach, assuming that patients who discontinue double-blind treatment early would have similar Worst Itching Intensity NRS scores as other patients in their respective treatment arm that have complete data:

- Intermittent missing NRS scores 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.
- NRS scores missing after patients discontinue study drug early will then be multiply imputed with the SAS MI procedure using a method appropriate for

monotone missingness (eg, regression statement). Details on the MI procedure can be found in Appendix 14.6.

- The proportion of patients who have an improvement from baseline with respect to the weekly mean of the daily 24-hour Worst Itching Intensity NRS score ≥3 points will be calculated for each imputed dataset. Differences between CR845 0.5 mcg/kg and placebo with respect to the primary endpoint will be compared using a logistic regression model containing terms for treatment group, baseline NRS score, use of prior anti-itch medication, presence of specific medical conditions, and country/region.
- Results of the logistic regression on the multiply imputed data sets will be summarized by the SAS MIANALYZE procedure.

The final p-value will be calculated using the Cui, Hung, Wang (CHW) procedure where the z-score is a weighted average of the z-score at the interim and the z-score observed for data collected after the interim, following the formula below.

$$Z_{final}=Zi_{nterim} * \sqrt{(n/N)} + Z_{post\text{-}interim} * \sqrt{(1- n/N)}$$

where n is the number of patients at the interim and N is the initial number of patients planned (300).

Sensitivity analyses of the primary efficacy endpoint will be conducted to evaluate the robustness of study results under different assumptions and imputation algorithms. For each of these sensitivity analyses, the final p-value will be calculated based on the CHW procedure, using the formula specified above.

- **Sensitivity 1:** Early discontinuations as nonresponders

  Patients who discontinue study drug early will be considered nonresponders. The imputed data will be analyzed using a logistic regression model similar to the primary analysis.

- **Sensitivity 2:** Multiple imputation; missing not at random (MNAR)

  This sensitivity analysis is an implementation of a pattern mixture model that draws from different populations based on the reason for withdrawal.

  - Intermittent missing NRS scores will first be imputed using the MCMC method with the SAS MI procedure, which is appropriate for non-monotonic missing data.
  - For patients who discontinued study drug due to adverse events, NRS scores missing after discontinuation will be imputed using the distribution of the baseline value of all patients' daily worst itching score assuming a trimmed normal (from 5 to 10).
  - For patients who discontinue due to reasons other than adverse event, missing NRS scores after patients discontinue study drug early will be multiply

imputed using multiple calls of the SAS MI procedure using data from patients within the same treatment group that have complete data at that time. The proportion of patients who have an improvement from baseline with respect to the weekly mean of the daily 24-hour Worst Itching Intensity NRS score ≥3 points will be calculated for each imputed dataset

- Similar to the primary analysis, results of the logistic regression on the multiply imputed data sets will be summarized by the SAS MIANALYZE procedure.

- **Sensitivity 3:** Tipping point analysis

  Multiple imputation with mixed missing data mechanisms (MNAR for a missing data pattern and MAR for others) will be used to assess the robustness of the MAR assumption. This sensitivity analysis is to investigate the departure from MAR assumption by progressively decreasing the treatment differences with respect to the NRS scores over the missing visits in active treatment group until conclusion from the primary analysis is overturned. The MI procedure includes the following steps:

  - Uses MCMC methodology from PROC MI by treatment group to impute the intermittent missing data to a monotone missing pattern
  - Uses a standard MAR-based MI approach from PROC MI to impute data from monotone missing data
  - For patients in the active treatment group, shift parameter from PROC MI will be progressively applied to impute the missing data, until the p-value >0.05

To evaluate the potential impact of the IA on the properties of statistical inference at the end of the trial, the primary and sensitivity analyses of the primary endpoint will also be presented separately for the sample of patients enrolled into the study after the IA.

8.7.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are the:

- Proportion of patients achieving ≥4-point improvement from baseline with respect to the weekly mean of the daily 24-hour Worst Itching Intensity NRS at Week 12 (Day 79 to 85) of the Double-blind Treatment Period;
- Proportion of patients achieving ≥3-point improvement from baseline with respect to the weekly mean of the daily 24-hour Worst Itching Intensity NRS at Week 8 of the Double-blind Treatment Period;
- Proportion of patients achieving ≥3-point improvement from baseline with respect to the weekly mean of the daily 24-hour Worst Itching Intensity NRS at Week 4 of the Double-blind Treatment Period;

- Proportion of patients achieving ≥4-point improvement from baseline with respect to the weekly mean of the daily 24-hour Worst Itching Intensity NRS at Week 8 of the Double-blind Treatment Period;
- Proportion of patients achieving ≥4-point improvement from baseline with respect to the weekly mean of the daily 24-hour Worst Itching Intensity NRS at Week 4 of the Double-blind Treatment Period;
- Change from baseline in itch-related quality of life at the end of Week 12 of the Double-blind Treatment Period, as assessed by the Skindex-10 Scale total score;
- Change from baseline in itch-related quality of life at the end of Week 12 of the Double-blind Treatment Period, as assessed by the 5-D Itch Scale total score.

The proportion of patients achieving ≥4-point improvement from baseline at Week 12 of the Double-blind Treatment Period, the proportion of patients achieving ≥3-point improvement from baseline at Week 8 and Week 4, and the proportion of patients achieving ≥4-point improvement from baseline at Week 8 and Week 4 with respect to the weekly mean of the daily 24-hour Worst Itching Intensity NRS will be analyzed following a methodology similar to the one employed for the primary analysis of the primary endpoint.

The Skindex-10 Scale total score and the 5-D Itch Scale total score change from baseline at Week 12 will be analyzed using an analysis of covariance (ANCOVA) model that will contain treatment as fixed effect, with baseline score, region, and the randomization stratification variables as covariates. The baseline 5-D total score and the Skindex-10 total score will be defined as the value collected on Day 1, prior to randomization.

For each domain in each questionnaire, missing values at Week 12 will be imputed using an MI approach, assuming that patients who discontinue double-blind treatment early would have similar domain scores as other patients in their respective treatment arm that have complete data:

- Intermittent missing scores 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;
- The monotone missing values will then be multiply imputed with the SAS MI procedure using the monotone regression method;
- For each stage, MI will be performed within treatment group with covariates for baseline score, region, both randomization stratification factors, and all non-missing visit scores for each domain of the questionnaire;
- For each questionnaire, the total score at each visit will be computed from the domain scores for each imputed dataset;

- The ANCOVA analysis described above will be implemented for each imputed dataset. Results of the ANCOVA on the multiply imputed data sets will be summarized by the SAS MIANALYZE procedure.

The LS means, standard errors, 95% CIs, and differences between treatment groups reported with LS means, standard errors, and 95% CIs derived from the ANCOVA on the imputed datasets will be reported.

Additionally, a sensitivity analysis of the 5D Itch scale and the Skindex-10 scale will be performed to describe the time course of the treatment response over the 12-week treatment period using a mixed effects model with repeated measures (MMRM). The model will contain treatment, week, and treatment-by-week interaction as fixed effects; baseline score, prior anti-itch medication usage, presence of specific medical conditions, and country/region as covariates. Repeated measures will include values collected at the end of Weeks 4, 8, 10, and 12 (end of treatment). It is important to note that, in HD patients, the study drug administered during the last dialysis of a particular week is not cleared until the first dialysis of the next week. Therefore, measurements that would reflect treatment effect at the end of a specific week (eg. Week 4) will actually be collected during the first day of the next week (eg, Week 5).

An unstructured covariance matrix will be used to model the within-subject errors. Should the model fail to converge, a compound symmetric covariance matrix will be used instead. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. Missing scores will not be imputed. Assuming that the data are MAR, the estimates of the treatment differences calculated from the MMRM described above are unbiased.

Standard descriptive statistics will be reported for each time point on the values and changes from baseline along with the least squares (LS) means, standard errors, 95% CIs and differences between treatment groups reported with LS means, standard errors, and 95% CIs.

8.7.3 Hypothesis Testing Strategy

The efficacy of CR845 0.5 mcg/kg compared to placebo in pivotal Phase 3 study CLIN3103 will be evaluated based on 1 primary and 7 secondary efficacy endpoints.

Testing of the primary efficacy endpoint will be 2-sided and conducted at the 5% error level. The study will be considered positive if the null hypothesis of no treatment difference in the primary efficacy analysis of the primary endpoint (proportion of patients achieving ≥3-point improvement from baseline with respect to the Worst Itching Intensity NRS) is rejected in favor of the alternative that patients randomized to CR845 experience significantly less itching compared to patients randomized to placebo.

To protect the Type 1 error, a gate-keeping strategy will be implemented. Although the p values corresponding to the hypothesis testing of the secondary variables will be reported, they will only be considered inferential if the primary analysis is statistically significant. Testing of the secondary efficacy endpoints will be performed sequentially at a 2-sided 5% error level in the order specified below. If the test of an endpoint in the sequence is not statistically significant, the p-value for the tests corresponding to the remaining endpoints in the sequence will not be considered inferential and the null hypotheses for the subsequent tests will not be rejected.

- Proportion of patients achieving ≥4-point improvement from baseline with respect to the weekly mean of the daily 24-hour Worst Itching Intensity NRS at Week 12 of the Double-blind Treatment Period;
- Proportion of patients achieving ≥3-point improvement from baseline with respect to the weekly mean of the daily 24-hour Worst Itching Intensity NRS at Week 8 of the Double-blind Treatment Period;
- Proportion of patients achieving ≥3-point improvement from baseline with respect to the weekly mean of the daily 24-hour Worst Itching Intensity NRS at Week 4 of the Double-blind Treatment Period;
- Proportion of patients achieving ≥4-point improvement from baseline with respect to the weekly mean of the daily 24-hour Worst Itching Intensity NRS at Week 8 of the Double-blind Treatment Period;
- Proportion of patients achieving ≥4-point improvement from baseline with respect to the weekly mean of the daily 24-hour Worst Itching Intensity NRS at Week 4 of the Double-blind Treatment Period;
- Change from baseline in Skindex-10 Scale total score at Week 12 of the Double-blind Treatment Period;
- Change from baseline in 5-D Itch Scale total score at Week 12 of the Double-blind Treatment Period.

8.7.4 Additional Efficacy Endpoints

8.7.4.1 Itch-intensity Measures

- Proportion of patients who have an improvement from baseline at Week 12 of the Double-blind period with respect to the weekly mean of the 24-hour Worst Itching Intensity NRS scores ≥1 and ≥2. The calculation of the proportions will be based on the NRS data using a multiple imputation (MI) approach for the missing data as in the primary efficacy analysis. A figure presenting the proportion of patients who have an improvement from baseline in NRS scores at Week 12 that is ≥1, ≥2, ≥3, and ≥4 will be prepared.
- Change from baseline in the weekly mean of the 24-hour Worst Itching Intensity NRS score at each week of the Double-blind Treatment Period (Week 1 to

Week 12). Treatment differences between CR845 and placebo at each postbaseline time point will be evaluated using the same MMRM detailed in Section 8.7.2.

- Proportion of patients who rate their itch condition as "Very much improved" or "Much Improved" at the end of Week 12 of the Double-blind Treatment Period/end of double-blind treatment, as measured by the Patient Global Impression of Change. Treatment difference will be tested using the Cochran-Mantel-Haenszel test, adjusting for strata. An exact test, such as the Fisher's Exact Test, may be used if the observed count in a particular cell is small (ie, <5).

8.7.4.2 Itch-related Quality-of-Life Measures

Itch-related quality-of-life measures and their analyses will include:

- Change from baseline in itch-related quality of life at each week of the Double-blind Treatment Period, as assessed by the 5-D Itch Scale total score. Treatment differences between CR845 and placebo at each postbaseline time point will be evaluated using the same MMRM fitted for the secondary efficacy analysis.
- Change from baseline in itch-related quality-of-life at each week of the Double-blind Treatment Period, as assessed by the Skindex-10 Scale total score. Treatment differences between CR845 and placebo at each postbaseline time point will be evaluated using the same MMRM fitted for the secondary efficacy analysis.
- Change from baseline in itch-related quality of life at Week 12 of the Double-blind Treatment Period and at each of the remaining weeks of the Double-blind Treatment Period with respect to each of the 3 domains of the Skindex-10 Scale. Treatment differences with respect to each domain will be evaluated using a model similar to the MMRM fitted for the analysis of the change from baseline in the overall Skindex-10 Scale score (Section 8.7.2).

8.8 Safety Analysis

Analysis of all safety data collected during the Double-blind Phase will be performed on the Double-blind Safety Population. The SAP will provide further detail for the analyses to be applied to each safety parameter, and will also include analyses of safety data collected during the Open-label Extension Phase and during exposure to CR845 during both the Double-blind and Open-label Extension Phases. No statistical hypothesis testing will be carried out and no inferential statistical analysis of the safety parameters will be performed.

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

8.8.1 Exposure to Study Drug

For this study, the duration of double-blind treatment for each individual patient may be up to 12 weeks, for a total of approximately 36 doses of study drug administered immediately following each dialysis session. Day 1 of the Double-blind Treatment Period will be defined as the day of administration of the first dose of study drug. The last day of the Double-blind Treatment Period will be defined as the day of the dialysis session immediately following the last injection of study drug.

Exposure and treatment compliance during the Double-blind Treatment Period will be summarized by the following parameters:

- Duration of treatment (days)
- Total number of doses actually received
- Number of missed doses

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

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

8.8.2 Adverse Events

All adverse events, as reported by the site, will be coded using MedDRA to MedDRA SOC and Preferred Term for standardization and summary purposes.

All reported adverse events (whether or not treatment-emergent) will be included in a by-patient adverse event listing. Only TEAEs will be included in summary tables which will present results by treatment group and by study period, as appropriate.

Adverse events that are considered “treatment emergent” relative to the Run-in Period are identified as any adverse event with an onset date after the start of the Run-in Period and up to the first dose of study drug during the Double-blind Period.

Adverse events that are considered “treatment emergent” relative to the Double-blind Period are identified as any adverse event

- with an onset date after the first dose of the double-blind study drug up to the Follow-up Visit or Early Termination Visit (or 7 to 10 days after the last dose if no Early Termination Visit was conducted), whichever is later, for patients who do not enter the Open-label Extension Phase.

- with an onset date after the first dose of the double-blind study drug up to the first dose of open-label drug for patient who continue into the Open-label Extension Phase.

The number and percentage of patients experiencing TEAEs will be summarized by treatment group and by period. A patient will be counted only once in the incidence count for a MedDRA SOC or Preferred Term, although a patient may have multiple occurrences (start and stop) of an event associated with a specific MedDRA Preferred Term or SOC. The most frequent TEAEs (≥5% of patients in any treatment group) will also be tabulated by SOC and Preferred Term.

The incidence and percentage of patients experiencing treatment-emergent SAEs and TEAEs leading to study discontinuation will be presented by the appropriate MedDRA SOC and Preferred Term. Adverse events that result in death will also be summarized.

Treatment-emergent adverse events will also be summarized by severity for each study period of the Double-blind Phase and by relationship to double-blind study drug for the Double-blind Period. If the severity and/or relationship to the study drug of an adverse event is missing, a worst-case scenario will be assumed (ie, the adverse event will be categorized as "severe" and/or "related" to the study drug). If a patient reports the same TEAE multiple times the event with the worst severity and the strongest relationship to study drug will be tabulated.

For each period of the Double-blind Phase, an overall summary table will be provided, presenting for each treatment group: the number and percentage of patients with an adverse event (both treatment and non-treatment emergent) during that period, a TEAE, serious TEAE, related TEAE, severe TEAE, TEAE leading to dose interruption, and TEAE leading to study drug discontinuation. This table will also include the number of events for each specific Preferred Term.

All adverse events will be listed in chronological order, including patient identifier, age, race, gender, a flag indicating whether the event was treatment-emergent, and all related event status information (start and stop dates, whether the event was ongoing, study day of onset, severity, seriousness, relationship to study medication, action taken with study treatment, and outcome). Separate listings will be generated for SAEs, deaths, and adverse events leading to study drug discontinuation. Additionally, a coding list of Preferred Terms and the verbatim text associated with them will be produced.

8.8.3 Clinical Laboratory Evaluations

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

All laboratory evaluation summaries will include the patients in the Double-blind Safety Population who have at least 1 postbaseline time point (for criteria based on postbaseline

assessments) and with both a baseline and at least 1 postbaseline time point (for criteria evaluating changes from baseline).

Laboratory values will be reported in Système International units.

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

Additionally, alanine aminotransferase, aspartate aminotransferase, bilirubin, and alkaline phosphatase will be presented in a separate listing, with 3× and 5×ULN flagged for alanine aminotransferase and aspartate aminotransferase; 2×ULN flagged for bilirubin, and 1.5×ULN flagged for alkaline phosphatase.

8.8.4 Vital Signs and ECGs

Summary tables will include descriptive statistics for baseline and each postbaseline assessment. Descriptive statistics will be calculated on both the actual score and the change from baseline score. Baseline is defined as the last measurement taken on or prior to the first day of dosing. Note that the Day 1 assessment can be included in the evaluation of baseline if that the assessment is performed prior to dosing.

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

Clinically notable vital signs will be identified based on the criteria defined in the SAP. For each vital sign parameter, the number and percentage of patients with at least 1 notable value will be tabulated by week and overall for the Double-blind Phase.

All vital signs will be listed in by-patient listings, including visit and collection date/time, and will be sorted by patient identifier and date/time of assessment.

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

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

8.9 Additional Analyses

8.9.1 Inflammatory Biomarkers

The observed value and the change in inflammatory biomarkers (eg, IL-6, IL-8, and granulocyte macrophage-colony stimulating factor) from pre-dose to the end of the Double-blind Treatment Period (Week 12) will be presented by treatment group. Univariate and multivariate analyses of the change in inflammatory biomarkers will be described in an analysis plan, separate from the study SAP.

8.9.2 Missed Dialysis Visits and Incidence of Infection

The number and percentage of patients who missed 1 or more dialysis visits during the Double-blind Treatment Period, and the total number of missed dialyses visits will be tabulated overall and by treatment group.

Incidence of infections based on adverse events, hospitalizations, and/or use of antibiotics for treatment of infection related to uremic pruritus will be analyzed using Fisher's Exact Test.

9.0 Quality Control and Quality Assurance

9.1 Study Monitoring Plan

Monitoring and auditing procedures that comply with current Good Clinical Practice (GCP) guidelines will be followed, including remote and onsite review of the eCRFs via an electronic data capture system for completeness and clarity, source document verification, evaluation of protocol adherence, appropriate documentation of informed consent procedures, safety reporting, study drug storage, and dispensation. The study will be monitored by the Sponsor or its designee (contract research organization). Monitoring will be performed by a representative of the Sponsor or its designee (site monitor) who will review patient enrollment, eCRFs, source documents, drug accountability records, and reporting and recording of adverse events. The site monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent site visits and communications (letter, telephone, and facsimile).

The site monitor(s) will follow written standard operating procedures as agreed with the contract research organization and the Sponsor. The site monitor(s) will verify that the clinical study is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements. Monitoring reports will be submitted to the Sponsor in a timely fashion as per details described in a clinical monitoring plan for this study.

Name and contact information for monitors will be included in the ISF.

9.2 Audits and Inspections

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

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

9.3 Data Collection, Validation, and Analysis

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

10.0 Ethics and Regulatory Compliance

10.1 Independent Ethics Committee or Institutional Review Board

A properly constituted, valid IRB or IEC and the national regulatory authority, if required by the applicable laws in the county, must review and approve the protocol, the Investigator's Brochure, ICF, and related patient information and recruitment materials (if applicable) before the start of the study. It is the responsibility of the Investigator to ensure that written informed consent is obtained from the patient before any activity or procedure is undertaken that is not part of routine care.

The IRB/IEC 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/IEC approval has been obtained.

If it is necessary to amend the protocol and/or ICF during the course of the study, the Investigator must ensure that the IRB/IEC and the national regulatory authority, if required by the applicable laws in the country, reviews and approves these amended documents. Except for changes necessary to eliminate an immediate hazard to study patients, or when the change involves only logistical or administrative aspects of the study (eg, change in monitor, change of telephone number), no amendments to the study protocol will be made without the prior written agreement of the Sponsor and acknowledgement by the Investigator and, as applicable, the IRB/IEC and the national regulatory authority, if required by the applicable laws in the country.

The Investigator(s) will maintain documentation of the composition of the IRB/IEC as well as all correspondence with the IRB/IEC. The Investigator(s) will comply with local requirements for routine reporting to the IRB/IEC as well as local and government requirements for notifying the IRB/IEC of SAEs. The Investigator will provide the Sponsor or its designee copies of all IRB/IEC approval notices, correspondence, annual reports, and final study progress reports.

10.2 Ethical Conduct of the Study

The study will be conducted in accordance with the provisions of the Declaration of Helsinki (October 2013), FDA (CFR, Sections 312.50 and 312.56), EU (536/2014) and UK regulations (The Medicines for Human Use [Clinical Trials] Regulations 2004 [No.1031]), ICH GCP (CPMP 135/95), and with the applicable regulations of the countries in which the study is conducted.

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

10.3 Informed Consent Process

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

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and that continues throughout the individual's study participation. The Investigator or designee will discuss extensively with the participant patient the study risks. Copies of the current, IRB/IEC-approved ICF detailing the risks and benefits of study participation will be provided to the participants. Consent forms describing in detail the study drug and study procedures/intervention and risks will be fully explained to the patient and written documentation of informed consent will be required prior to starting participation in the study. Upon reviewing the document, the Investigator or designee will explain the research study to the participant and answer any questions that may arise. The participants will sign the ICF prior to any procedures being performed 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. Participants must be re-consented to the most current version of the ICF during their participation in the study.

10.4 Patient Confidentiality

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

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

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

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

11.0 Data Handling and Quality Assurance

All participant data relating to the study will be recorded on eCRFs unless transmitted to the Sponsor or designee electronically (eg, laboratory data). No data are to be recorded directly in the eCRFs (eg, all data will have a unique source). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

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

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

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

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

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

12.0 Administrative Procedures

12.1 Protocol Adherence

It is vital to the success of the study that the Investigator adhere to the details of the protocol, and thus to keep to a minimum the number of cases later classified as "incomplete," "unusable," or "not evaluable." If, in the interest of safety and/or well-being of a particular patient, it is necessary to depart from the protocol, then that protocol deviation will pertain to that individual patient only and will be documented. Protocol deviations due to lack of patient compliance must also be documented.

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

12.2 Publication of Study Findings

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

13.0 References

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14.0 Appendix

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

New York Heart Association (NYHA) Classification of Heart Failure

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

[Criteria Committee of the New York Heart Association 1994]

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

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

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**

Date Completed:

D	D	M	M	M	Y	Y	Y	Y
					2	0		

Time:

☐☐ : ☐☐

☐ AM ☐ PM

SUBJECT INITIALS

First	*Middle*	*Last*

14.3 Appendix 3: Skindex-10 Scale

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

INSTRUCTIONS: 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	☐	☐	☐	☐	☐	☐	☐
2. The persistence/reoccurrence of your itching	☐	☐	☐	☐	☐	☐	☐
3. The appearance of your skin from scratching	☐	☐	☐	☐	☐	☐	☐
4. Frustration about your itching	☐	☐	☐	☐	☐	☐	☐
5. Being annoyed about your itching	☐	☐	☐	☐	☐	☐	☐
6. Feeling depressed about your itching	☐	☐	☐	☐	☐	☐	☐
7. Feeling embarrassed about your itching	☐	☐	☐	☐	☐	☐	☐
8. The effects of your itching on your interactions with others (for example: interactions with family, friends, close relationships, etc.)	☐	☐	☐	☐	☐	☐	☐
9. The effects of your itching on your desire to be with people	☐	☐	☐	☐	☐	☐	☐
10. The effect of your itching making it hard to work or do what you enjoy	☐	☐	☐	☐	☐	☐	☐

Date Completed:

					2	0		
D	D	M	M	M	Y	Y	Y	Y

Time:

☐☐ : ☐☐

☐ AM ☐ PM

SUBJECT INITIALS

First	*Middle*	*Last*

14.4 Appendix 4: 5-D Itch Scale

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

1.	DURATION:	During the last 2 weeks, how many hours a day have you been itching?				
		Less than 6 hrs/day ☐	6-12 hrs/day ☐	12-18 hrs/day ☐	18-23 hrs/day ☐	All day ☐
2.	DEGREE:	Please rate the intensity of your itching over the past 2 weeks				
		Not present ☐	Mild ☐	Moderate ☐	Severe ☐	Unbearable ☐
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 ☐
4.	DISABILITY:	Rate the impact of your itching on the following activities over the last 2 weeks				
	Sleep	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 ☐
		N/A	Never affects this activity	Rarely affects this activity	Occasionally affects this activity	Frequently affects this activity	Always affects this activity
	Leisure/Social	☐	☐	☐	☐	☐	☐
	Housework/ Errands	☐	☐	☐	☐	☐	☐
	Work/School	☐	☐	☐	☐	☐	☐

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

Date Completed:

☐☐ ☐☐☐ 2 0 ☐☐
D D M M M Y Y Y Y

Time:

☐☐ : ☐☐
☐ AM ☐ PM

SUBJECT INITIALS
First Middle Last
☐ ☐ ☐

14.5 Appendix 5: Patient Global Impression of Change

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

Since the start of the study, my itch is:

1. ☐ **Very much improved**
2. ☐ **Much improved**
3. ☐ **Minimally improved**
4. ☐ **Not changed**
5. ☐ **Minimally worse**
6. ☐ **Much worse**
7. ☐ **Very much worse**

Date Completed:									
					2	0			
D	D	M	M	M	Y	Y	Y	Y	

Time:	
☐☐ : ☐☐	
☐ AM ☐ PM	

SUBJECT INITIALS		
First	*Middle*	*Last*

14.6 Statistical Appendix

This appendix provides further details related to the treatment of missing data for the primary and sensitivity analyses of the primary endpoint.

For multiple imputations and other instances where random seeds are required, the values used (in order) are:

8392857
2985729
1843255
9086284
5547484
8017456
9597295
2252256
4821871
9852467
5126715
3232132
9841654
3645284
1587345

Note that not all seeds may be required in programming the multiple imputations. If additional seeds are needed, they will be chosen by adding 1 to each of the values above, again using them in order.

The number of imputations for the multiple imputations will be 20.

For the primary analysis, a multi-stage process will be applied:

Stage 1: Subjects will have their 11-point NRS scores imputed. First, using all visits, intermittent missing data will be imputed using the Markov Chain Monte Carlo (MCMC) method implemented with the SAS MI procedure; data imputed following subject discontinuation via this process will be censored out of the resulting dataset so that only intermittent missing data is imputed via this method. Second, monotone missing data will be imputed following subject discontinuation using SAS proc MI. For each stage, MI will be performed within treatment group with covariates for baseline NRS score, use of prior anti-itch medication, and presence of select medical conditions. Should convergence issues occur due to small cell size for the one or both of the categorical covariates at either stage, the appropriate covariate(s) will be removed from the model.

Stage 2: Using the resulting complete datasets, the change from baseline with respect to the 11-point NRS will be calculated; patients will be categorized as responder if they have a 3-point (or greater) improvement over baseline. Week 12 values will serve as the primary timepoint. The 20 MI runs will be analyzed independently using a logistic

model and the results combined using SAS proc MIANALYZE. Logistic model covariates will include treatment, baseline NRS score, use of prior anti-itch medication, and presence of select medical conditions. As with the MI, should convergence issues occur due to small cell sizes, the appropriate categorical covariate(s) will be dropped as necessary.

Should a sample size increase occur, the above process will be implemented completely independently among subjects contributing the interim results and those following the interim analysis.

For the tipping point analysis, a shift parameter will be applied to only subjects in the active group, running from 0 to 5 points in 0.25-point increments or until the conclusions of the analysis "tip" and the results are no longer significant. This analysis will not be performed should the initial primary results fail to achieve significance.