A MULTICENTER, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY TO EVALUATE THE SAFETY AND EFFICACY OF ORAL CR845 IN CHRONIC KIDNEY DISEASE PATIENTS WITH MODERATE-TO-SEVERE PRURITUS

Protocol number:	CR845-210301
Phase:	2
IND number:	132198
Protocol version:	Version 1.2
Date:	14 May 2018
Sponsor:	Cara Therapeutics, Inc. 4 Stamford Plaza Stamford, CT 06902 (203) 406-3700

SPONSOR APPROVAL / SIGNATURE PAGE

INVESTIGATOR APPROVAL STATEMENT

I have read and understand the protocol (CR845-210301) and I agree that this document contains all ethical, legal, and scientific information necessary to conduct this study. I will oversee the conduct of the study as described in the protocol and any amendment(s) made to the protocol.

I agree to conduct the study as detailed herein and in compliance with the current International Council for Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice E6 (R1), E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) Integrated, United States Code Title 21 (Food and Drug Administration), and applicable regulatory requirements.

Principal Investigator

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 Oral CR845 in Chronic Kidney Disease Patients with Moderate-to-Severe Pruritus
PROTOCOL NUMBER	CR845-210301
PHASE OF DEVELOPMENT	2
INVESTIGATIONAL PRODUCT	CR845 Tablets
NAME OF ACTIVE INGREDIENT	CR845
ROUTE OF ADMINISTRATION	Oral
STUDY CENTERS	Up to 80 sites
OBJECTIVES	Primary Objective • To evaluate the efficacy of 3 dose levels of oral CR845 compared to placebo in reducing the intensity of itch in chronic kidney disease (CKD) patients with moderate-to-severe pruritus. Secondary Objectives • To evaluate the efficacy of 3 dose levels of oral CR845 compared to placebo in improving itch-related quality-of-life measures in CKD patients with moderate-to-severe pruritus. • To evaluate the safety of 3 dose levels of oral CR845 in CKD patients with moderate-to-severe pruritus.
NUMBER OF PATIENTS	The planned sample size is approximately 240 (60 per treatment group) male and female CKD patients with moderate-to-severe pruritus (mean baseline 24-hour Worst Itching Intensity numerical rating scale (NRS) score ≥5). The sample size may be increased up to 480 patients (120 per treatment group) based on the results of a planned interim analysis (IA) conducted when approximately 50-60% of the planned 240 patients have been randomized and have either completed the 12-week Treatment Period or have discontinued study drug early. Randomization will be stratified according to the patient's renal disease status: moderate CKD non-dialysis; severe CKD non-dialysis; and severe CKD on dialysis (ie, 3 categories). The randomization of severe CKD patients on hemodialysis will be capped at approximately 20% of the total sample size (ie, 48 of 240 patients).

STUDY POPULATION	**Inclusion Criteria:** To be eligible for inclusion into the study, a patient must meet the following criteria: 1. Willing and able to provide written informed consent prior to participating in this study; 2. Able to communicate clearly with the Investigator and staff, able to understand the study procedures, and able and willing to comply with the study requirements; 3. Male or female 18 years of age or older; 4. CKD patients with stage III, IV, or V disease (ie, moderate renal impairment with estimated glomerular filtration rate (GFR) ≥30 and <60 mL/min/1.73 m^2 or severe renal impairment with estimated GFR <30 mL/min/1.73 m^2). For severe CKD patients on hemodialysis, they must be receiving hemodialysis 3 times per week for at least 3 months prior to the start of screening; **Note 1:** Patients who have received a renal organ transplant and who are at least 6 months post-transplant with an estimated GFR <60 mL/min/1.73 m^2 may participate if clinically stable and are on maintenance immunosuppression. **Note 2:** Severe CKD patients on hemodialysis who require an additional hemodialysis treatment to manage fluid overload may be enrolled as long as it is anticipated that no more than 1 such treatment will be required in any given week. **Note 3:** Severe CKD patients on hemodialysis receiving in-home hemodialysis may participate as long as they have switched to in-center hemodialysis at least 2 weeks prior to screening and plan to remain on in-center hemodialysis for the duration of the study. 5. If female, is not pregnant or nursing during any period of the study; 6. If female: a. is surgically sterile; or b. has been amenorrheic 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 body weight between 40.0 and 140.0 kg, inclusive (for severe CKD patients on hemodialysis, this is the prescription dry body weight); 9. Self-reports experiencing daily or near-daily pruritus during the month prior to screening; 10. For severe CKD patients on hemodialysis, at least 2 single-pool Kt/V measurements ≥1.2, 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-month period prior to screening; 11. Prior to randomization: a. Has completed at least 4 Worst Itching Intensity NRS worksheets from the start of the 7-day Run-in Period; 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.

	Exclusion Criteria: A patient will be excluded from the study if any of the following criteria are met: 1. Patients not currently on dialysis who are likely to initiate routine dialysis during study participation; 2. For severe CKD patients on hemodialysis, noncompliance with hemodialysis treatment that, in the opinion of the Investigator, would impede completion or validity of the study; 3. Scheduled to receive a kidney transplant during the study; 4. Has a concomitant disease or any medical condition that, in the opinion of the Investigator, could pose undue risk to the patient, impede completion of the study procedures, or would compromise the validity of the study measurements, including, but not limited to: a. Known or suspected history of 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; 5. New or change of treatment received for itch including antihistamines and corticosteroids (oral, intravenous [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. Serum alanine aminotransferase or aspartate aminotransferase greater than 2.5 times the reference upper limit of normal (ULN), or total bilirubin greater than 2 times the ULN at screening; 8. 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; 9. Has pruritus attributed to a cause other than CKD (eg, patients with concomitant pruritic dermatological disease or cholestatic liver disease would be excluded); 10. Has localized itch restricted to the palms of the hands; 11. Anticipates receiving an opioid antagonist (eg, naloxone, naltrexone) or opioid-mixed agonist-antagonist

	(eg, buprenorphine, nalbuphine) from the start of screening through the end of the Treatment Period; 12. Received ultraviolet B treatment within 30 days prior to the start of screening or anticipates receiving such treatment during the study; 13. Participated in a previous clinical study with CR845. 14. If currently a patient with a renal transplant: a. Has received an increase or a new immunosuppressive treatment due to an acute or chronic rejection episode 4 weeks prior to screening; b. Is anticipated to have a change in immunosuppressive treatment from screening to the end of the study.
STUDY DESIGN	This is a multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of 3 dose levels (0.25, 0.5, and 1 mg) of oral CR845 in moderate-to-severe CKD patients with moderate-to-severe pruritus. This study will consist of a Screening Period, a 7-day Run-in Period, a 12-week Treatment Period, and a Follow-up Visit (approximately 7 days after the last dose of study drug). Informed consent will be obtained prior to performing any study-specific procedures. Screening will occur within 7 to 28 days prior to randomization to assess eligibility. Eligible patients will complete a 7-day Run-in Period during the week prior to randomization when they will be required to complete at least 4 Worst Itching Intensity NRS scale worksheets. The mean baseline Worst Itching Intensity NRS score during the 7-day Run-In Period must be ≥5. The mean baseline is defined as the average of all non-missing scores reported from the start of the 7-day Run-in Period. For consistency, patients will be requested to complete the Worst Itching Intensity NRS worksheets at a similar time each day. Patients will also be trained on the Skindex-10 Scale, 5-D Itch Scale, Patient Global Impression of Worst Itch Severity, and Patient Global Impression of Change (PGIC) worksheets at any time during the Run-in Period or on Day 1 of the Treatment Period. Day 1 of the Treatment Period will be defined as the day of the administration of the first dose of study drug. 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 in a 1:1:1:1 ratio to receive orally once daily either placebo or CR845 tablets at doses of 0.25, 0.5 or 1 mg. Randomization will be stratified according to the patient's renal disease status. Patients will report their Worst Itching Intensity NRS score over the last 24 hours daily during the entire Treatment Period. Patients will be instructed to complete the NRS score at a similar time of the day. In addition, patients will complete other patient-reported outcome (PRO)

	measures (Skindex-10 Scale, 5-D Itch Scale, Patient Global Impression of Worst Itch Severity) during the Treatment Period. The PGIC will be completed at end of treatment/early termination. Safety assessments tests will be conducted periodically starting at Screening until the Follow-up Visit. Adverse events and concomitant medications will be recorded during the study starting at Screening until the Follow-up Visit. A final safety Follow-up Visit will be conducted 7 to 10 days after the last dose of study drug.
STUDY DRUG	CR845 will be provided as enteric-coated tablets. All tablets are white in color with no markings and are identical in appearance, regardless of dose. CR845 tablets will be provided at doses of 0.25, 0.5, and 1 mg.
REFERENCE PRODUCT	Placebo to match CR845 tablets
TREATMENT REGIMENS	Patients will take study drug once daily for a total of 12 weeks. Each dose should be taken at least 2 hours prior to or after a meal, around the same time of day (patient should not lie down for at least 1 hour after swallowing the tablet). For severe CKD patients on hemodialysis, the study drug should not be taken until after their dialysis procedure on days when they receive dialysis. Note that the same requirement for meal timing of study drug must also be followed.
STUDY DURATION	Screening Period: Day -28 to Day -7 Run-in Period: 1 week prior to randomization (Day -7 to Day -1) Treatment Period: 12 weeks Follow-up Visit: 7-10 days after the End-of-Treatment Visit or Early Termination Visit Total study duration for a single patient: up to approximately 17 weeks
STUDY ENDPOINTS	<u>Efficacy Endpoints</u> **Primary Efficacy Endpoint** • Change from baseline with respect to the weekly mean of the daily 24-hour Worst Itching Intensity NRS score during Week 12 of the Treatment Period. **Secondary Efficacy Endpoints** • Change from baseline in itch-related quality of life at the end of Week 12, as assessed by the total Skindex-10 Scale score; • Change from baseline in itch-related quality of life at the end of Week 12, as assessed by the 5-D Itch Scale score; • Proportion of patients achieving an improvement from baseline ≥3 points with respect to the weekly mean of the daily 24-hour

	Worst Itching Intensity NRS score at Week 12 of the Treatment Period. Additional efficacy endpoints are described in Section 8.6.4. Safety Assessments The safety assessments used to evaluate the overall safety of CR845 will include adverse events, vital signs, 12-lead ECGs, and clinical laboratory evaluations.
INTERIM ASSESSMENT	An unblinded IA will be conducted when approximately 50-60% of the planned 240 patients have been randomized and have either completed the 12-week Treatment Period or have discontinued study drug early. The primary goal of the IA is to identify dose(s) of oral CR845 that are both safe and efficacious. Doses that are found to be unsafe or poorly tolerated will be dropped from the study. The sample size of any dose group that is found to be efficacious may be increased to ensure that the pairwise comparison against placebo with respect to the primary efficacy variable at the end of the study is powered appropriately. The sample size of dose groups that do not separate from placebo at the IA may not be increased; however, no dose will be dropped for futility reasons. The sample size will not be increased past 480 total patients (120 patients per treatment group). Details of the IA will be included in a separate document.

STATISTICAL ANALYSIS	**Analysis Populations** The Enrolled Population is defined as the group of patients who sign the informed consent form. The Safety and Full Analysis Populations are both defined as the group of all randomized patients who receive at least 1 dose of study drug. Following the intent-to-treat principle, patients in the Full Analysis Population will be analyzed according to their randomized treatment, regardless of the actual treatment received. Patients in the Safety Analysis Population will be analyzed according to their actual treatment. The Per-Protocol Population is defined as the subset of patients in the Full Analysis Population who do not have any major protocol deviations that could affect the efficacy analyses. Inclusion in the Per-Protocol Population will be determined prior to unblinding the data and will be detailed in the statistical analysis plan.
	Efficacy Analyses All efficacy analyses will be conducted using the Full Analysis Population. An analysis of the primary and secondary efficacy variables for the Per-Protocol Population may be performed if more than 20% of the patients in the Full Analysis Population are excluded. *Primary Efficacy Endpoint* The primary efficacy endpoint is defined as the change from baseline to Week 12 of the Treatment Period with respect to the weekly mean of the daily 24-hour Worst Itching Intensity NRS score. The weekly mean of the 24-hour Worst Itching Intensity NRS score will be defined as the sum of the daily Worst Itching Intensity NRS score reported during a specific week during the Treatment Period (eg, Days 2 to 8, Days 9 to 15, Days 16 to 22, etc.) divided by the number of days with non-missing scores for that week. If the daily worst itching score is missing for >3 days during a specific week, the corresponding weekly mean worst itching score will be set to missing. The baseline score will be defined as the average of the daily 24-hour Worst Itching Intensity NRS scores over the last 7 days prior to randomization,; at least 4 completed Worst Itching Intensity NRS worksheets will be required prior to randomization. The primary efficacy variable will be analyzed using a mixed effects model with repeated measures (MMRM). The model will contain treatment, week, and treatment-by-week interaction as fixed effects; baseline score and renal disease status as covariates, and patient as a random effect. For each dose group, the treatment group difference vs placebo will be estimated as the simple contrast in the treatment effect at Week 12 of the Treatment Period.

	In the primary efficacy analysis, missing NRS data will be imputed using a multiple imputation (MI) approach, assuming that patients who discontinue study drug early would have similar Worst Itching Intensity NRS scores as other patients in their respective treatment arm that have complete data. Sensitivity analyses of the primary efficacy endpoint will be conducted to evaluate the robustness of study results under different assumptions and imputation algorithms (Section 8.6.1).
	Secondary Efficacy Endpoints The Skindex-10 Scale total score and the 5-D Itch Scale total score will be analyzed using an MMRM that will contain treatment, week, and treatment-by-week interaction as fixed effects, baseline score and renal disease status as covariates, and patient as a random effect. Repeated measures will include values that reflect the Skindex-10 and the 5-D total scores at the end of Weeks 4, 8, 10, and 12 (end of treatment). The baseline value will be defined as the value of the Skindex-10 or 5-D total score collected on day 1 prior to randomization. Missing Skindex-10 Itch Scale and 5-D Itch Scales total scores will not be imputed. The mean treatment difference between each CR845 dose and placebo will be estimated as the simple contrast in the treatment effect at Treatment Period Week 12. The proportion of patients achieving an improvement from baseline ≥3 points with respect to the weekly mean of the daily 24-hour Worst Itching Intensity NRS score at Week 12 of the Treatment Period will be analyzed using logistic regression with terms for treatment group, baseline NRS score, and renal disease status. Missing NRS data will be imputed using the same methodology described for the primary efficacy endpoint. *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 is rejected in favor of the alternative that patients randomized to CR845 experience significantly less itching, as measured by the change from baseline to Week 12 of the Treatment Period with respect to the weekly mean of the 24-hour Worst Itching Intensity NRS score. This is a Phase 2 study designed to identify a safe and efficacious dose; therefore, each CR845 dose group will be compared against placebo. There will be no adjustment for multiple comparisons. **Safety Analyses** Analysis of all safety data will be performed using the Safety Population. Safety data will be summarized descriptively. No

	inferential statistics are planned. Analyses of safety data will include summaries of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and adverse events resulting in study drug discontinuation. Vital signs, clinical laboratory data, and ECG data will be descriptively summarized by visit as applicable, in addition to change from baseline.

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3.0 List of Abbreviations

ATC	Anatomical Therapeutic Chemical
CKD	chronic kidney disease
CNS	central nervous system
ECG	electrocardiogram
eCRF	electronic case report form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	glomerular filtration rate
H	above the laboratory parameter's reference range
IA	interim analysis
ICF	informed consent form
ICH	International Council for Harmonisation
IRB	Institutional Review Board
IV	intravenous
IVRS/IWRS	interactive voice or web response system
KOR	kappa-opioid receptor
L	below the laboratory parameter's reference range
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MMRM	mixed effects model with repeated measures
N	within the laboratory parameter's reference range
NRS	numerical rating scale
PGIC	Patient Global Impression of Change
PRO	patient-reported outcome
SAE	serious adverse event
SAP	statistical analysis plan
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 or references for details). An opioid analgesic like morphine acts primarily via activation of the mu-opioid receptor located in the CNS and peripheral nervous system, and as such, is associated with a wide array of side effects, including sedation, respiratory depression, abuse liability, and constipation. CR845 was designed to activate KORs located primarily in the peripheral nervous system, which are known to modulate itch, pain, and inflammatory signals, without producing the side effects associated with the activation of mu-opioid receptors, such as respiratory depression, abuse liability, and constipation.

CR845 is a potent and selective KOR agonist with more than 30,000-fold selectivity over mu- and delta-opioid receptors and does not demonstrate activity at other receptors, ion channels, or transporters. The unique peptidic structure of CR845 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 centrally-acting kappa agonists. Thus far, CR845 has no abuse properties and no respiratory depression effects (see Investigator's Brochure for details).

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. Though renal transplantation may ameliorate pruritic symptoms, up to 38% of renal transplant recipients may have persistent itching [Panuccio, 2017]. 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].

Based on nonclinical pharmacological studies, it was anticipated that CR845 will produce a combined anti-itch and anti-inflammatory effect (see Investigator's Brochure for details), which could provide significant relief of itch in patients with chronic kidney disease.

4.2 Clinical Experience

To date, more than 1300 healthy volunteers and patients have been exposed to CR845 either as an intravenous (IV) or oral formulation. The oral formulation of CR845 has been evaluated in 626 patients and healthy volunteers across three Phase 1 studies (including 1 study in hemodialysis patients) and two Phase 2 studies in patients with osteoarthritis. CR845 has been evaluated as single or repeated enteric-coated tablets or capsules at dosage strengths ranging from 0.1 to 10 mg and with tablets of 1, 2.5, and 5 mg administered twice daily for 8 weeks in osteoarthritis patients (Study CR845-CLIN2002-PO). In a Phase 1 study with hemodialysis patients, CR845 tablets at doses ranging from 0.25 to 1 mg administered either once after each dialysis session for 1 week (ie, 3 times) or once daily for 1 week was shown to be well-tolerated (Study CR845-CLIN1301). A recent Phase 1 study conducted in patients with moderate or severe chronic kidney disease (Stage III, IV, or V, not on maintenance dialysis) has also demonstrated that once-daily oral administration of CR845 was safe and well tolerated at doses of 0.25, 0.5, and 1 mg over a 1-week treatment period (Study CR845-CLIN1303).

4.3 Summary of Potential Risks and Benefits

The potential benefit of CR845 in alleviating the symptoms of pruritus associated with chronic kidney disease (CKD) in hemodialysis patients is predicated on its pharmacological class and evidence of its effectiveness in multiple animal models of pruritus and in two Phase 2 clinical studies with IV CR845 in hemodialysis patients experiencing moderate-to-severe pruritus (CR845-CLIN2005 Part B and CR845-CLIN2101).

In humans with normal renal function, CR845 has aquaretic effects that can result in dehydration and associated symptoms (eg, tachycardia) and hypernatremia if the fluid balance is not managed properly. However, these effects appear to be absent in the dialysis population, many of whom are anuric and all of whom have few functioning nephrons. These effects are also anticipated to be largely reduced in CKD patients stage III to IV not yet on dialysis.

Overall, tingling/numbness, dizziness, fatigue and/or drowsiness/somnolence have been the most common adverse events. Due to the potential adverse event of fatigue/drowsiness/somnolence, subjects should be cautioned about operating hazardous machinery or operating a motor vehicle.

Gastrointestinal dysfunction (abdominal discomfort, nausea, constipation) may be possible, as it has been frequently reported after oral tablet administration in normal healthy volunteers.

Tingling sensation or facial numbness has been reported shortly after administration of CR845. This effect is transient and does not appear to be a clinically significant issue.

While it has been demonstrated that CR845 has substantially less access to the CNS than previously tested kappa opioid agonists, adverse CNS effects of CR845 (eg, altered mental status) could still be considered a possibility (eg, hypothetically, in patients with impaired blood-brain barrier functioning).

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

5.0 Objectives

Primary Objective

- To evaluate the efficacy of 3 dose levels of oral CR845 compared to placebo in reducing the intensity of itch in CKD patients with moderate-to-severe pruritus.

Secondary Objectives

- To evaluate the efficacy of 3 dose levels of oral CR845 compared to placebo in improving itch-related quality-of-life measures in CKD patients with moderate-to-severe pruritus.
- To evaluate the safety of 3 dose levels of oral CR845 in CKD 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 3 dose levels (0.25, 0.5, and 1 mg) of oral CR845 in moderate-to-severe CKD patients with moderate-to-severe pruritus.

This study will consist of a Screening Period, a 7-day Run-in Period, a 12-week Treatment Period, and a Follow-up Visit (approximately 7 to 10 days after the last dose of study drug). Informed consent will be obtained prior to performing any study-specific procedures. Screening will occur within 7 to 28 days prior to randomization to assess eligibility.

Eligible patients will complete a 7-day Run-in Period during the week prior to randomization when they will be required to complete at least 4 Worst Itching Intensity numerical rating scale (NRS) worksheets. The mean baseline Worst Itching Intensity NRS score during the 7-day Run-in Period must be ≥5. The mean baseline is defined as the average of all non-missing scores reported from the start of the 7-day Run-in Period. For consistency, patients will be requested to complete the Worst Itching Intensity NRS worksheets at a similar time each day.

Patients will also be trained on the Skindex-10 Scale, 5-D Itch Scale, Patient Global Impression of Worst Itch Severity, and Patient Global Impression of Change (PGIC) worksheets at any time during the Run-in Period or on Day 1 of the Treatment Period.

Day 1 of the Treatment Period will be defined as the day of the administration of the first dose of study drug.

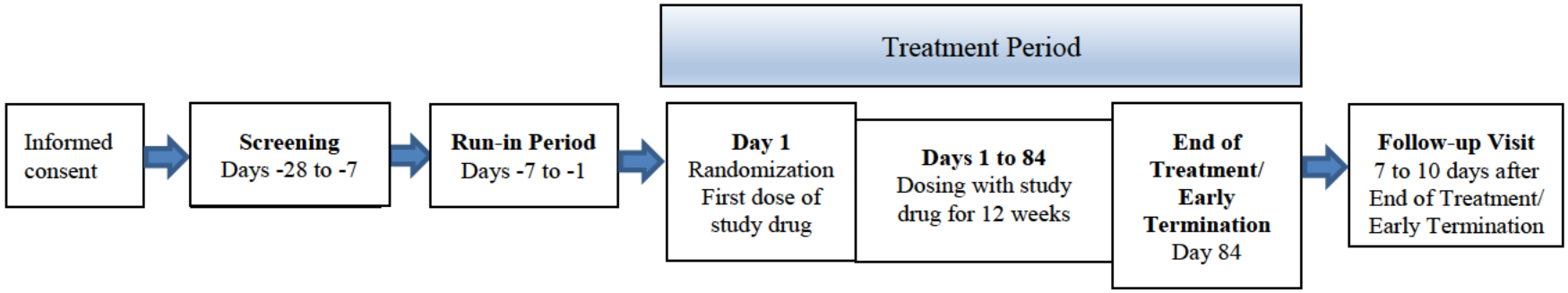
If patients continue to meet all inclusion and no exclusion criteria at the end of the 7-day Run-in Period, they will be randomized in a 1:1:1:1 ratio to receive orally once daily either placebo or CR845 tablets at doses of 0.25, 0.5 or 1 mg. Randomization will be stratified according to the patient's renal disease status: moderate CKD; severe CKD non-dialysis; severe CKD on dialysis (ie, 3 categories). The randomization of severe CKD patients on hemodialysis will be capped at approximately 20% of the total sample size (ie, 48 of 240 patients).

Patients will report their Worst Itching Intensity NRS score over the last 24 hours daily during the entire Treatment Period. Patients will be instructed to complete the NRS score at a similar time of the day throughout the Treatment Period. In addition, patients will complete other patient-reported outcome (PRO) measures (Skindex-10 Scale, 5-D Itch Scale, Patient Global Impression of Worst Itch Severity) during the Treatment Period. The PGIC will be completed at end of treatment/early termination.

Safety assessment will be monitored periodically as per schedule of events (Table 2). Adverse events and concomitant medications will be recorded during the study starting at Screening until the Follow-up Visit. A final safety Follow-up Visit will be conducted 7 to 10 days after the last dose of study drug.

The study schematic is shown in Figure 1.

Figure 1. **CR845-210301 Study Schematic**



6.2 Selection of Study Population

Patients with moderate-to-severe CKD, including patients who have received a renal organ transplant, 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 before enrollment, randomization, and dosing. All eligibility criteria must be met before a patient is enrolled.

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

6.2.1 Inclusion Criteria

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

1. Willing and able to provide written informed consent prior to participating in this study;
2. Able to communicate clearly with the Investigator and staff, able to understand the study procedures, and able and willing to comply with the study requirements;
3. Male or female 18 years of age or older;
4. CKD patients not currently maintained on hemodialysis with stage III, IV, or V disease (ie, moderate renal impairment with estimated glomerular filtration rate (GFR) ≥30 and <60 mL/min/1.73 m^2 or severe renal impairment with estimated GFR <30 mL/min/1.73 m^2). For patients with severe CKD on hemodialysis, they must be receiving hemodialysis 3 times per week for at least 3 months prior to the start of screening;
   Note 1: Patients who have received a renal organ transplant and who are at least 6 months post-transplant with an estimated GFR <60 mL/min/1.73 m^2 may participate if clinically stable and are on maintenance immunosuppression.
   Note 2: Severe CKD patients on hemodialysis who require an additional hemodialysis treatment to manage fluid overload may be enrolled as long as it is anticipated that no more than 1 such treatment will be required in any given week.
   Note 3: Severe CKD patients on hemodialysis receiving in-home hemodialysis may participate as long as they have switched to in-center hemodialysis at least 2 weeks prior to screening and plan to remain on in-center hemodialysis for the duration of the study.
5. If female, is not pregnant or nursing during any period of the study;
6. If female:
   a. is surgically sterile; or
   b. has been amenorrheic for at least 1 year and 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 body weight of between 40.0 and 140.0 kg, inclusive (for severe CKD patients on hemodialysis, this is the prescription dry body weight);
9. Self-reports experiencing daily or near-daily pruritus during the month prior to screening;
10. For severe patients on hemodialysis, at least 2 single-pool Kt/V measurements ≥1.2, 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-month period prior to screening;
11. Prior to randomization:
    a. Has completed at least 4 Worst Itching Intensity NRS worksheets from the start of the 7-day Run-in Period;
    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.

6.2.2 Exclusion Criteria

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

1. Patients not currently on dialysis who are likely to initiate routine dialysis during study participation;
2. For severe CKD patients on hemodialysis, noncompliance with hemodialysis treatment that, in the opinion of the Investigator, would impede completion or validity of the study;
3. Scheduled to receive a kidney transplant during the study;

4. Has a concomitant disease or any medical condition that, in the opinion of the Investigator, could pose undue risk to the patient, impede completion of the study procedures, or would compromise the validity of the study measurements, including, but not limited to:
    a. Known or suspected history of 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;
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. Serum alanine aminotransferase or aspartate aminotransferase greater than 2.5 times the reference upper limit of normal (ULN), or total bilirubin greater than 2 times the ULN at screening;
8. 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;
9. Has pruritus attributed to a cause other than CKD (eg, patients with concomitant pruritic dermatological disease or cholestatic liver disease would be excluded);
10. Has localized itch restricted to the palms of the hands;
11. Anticipates receiving an opioid antagonist (eg, naloxone, naltrexone) or opioid-mixed agonist-antagonist (eg, buprenorphine, nalbuphine) from the start of screening through the end of the Treatment Period;
12. Received ultraviolet B treatment within 30 days prior to the start of screening or anticipates receiving such treatment during the study;
13. Participated in a previous clinical study with CR845.
14. If currently a patient with a renal transplant:
    a. Has received an increase or a new immunosuppressive treatment due to an acute or chronic rejection episode 4 weeks prior to screening;
    b. Is anticipated to have a change in immunosuppressive treatment from screening to the end of the study.

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;
2. At the discretion of the Sponsor/Medical Monitor, if a patient receives a prohibited concomitant medication according to Table 1 (Section 6.4.7.2).

In addition, any patient who becomes pregnant during the Treatment Period or within 7 days after the last dose of study drug should be withdrawn from the study (Section 6.5.2.6).

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 after the last dose of study drug or, as soon as feasible. The Follow-up Visit is to be completed 7 to 10 days after the Early Termination Visit.

If study drug is discontinued, 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.

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

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

6.4 Treatments

6.4.1 Treatments Administered

Study drug (placebo tablet or CR845 tablet at a dose of 0.25, 0.5 or 1 mg) should be taken once daily at least 2 hours prior to or after a meal, around the same time of day (patient should not lie down for at least 1 hour after swallowing the tablet).

For severe CKD patients on hemodialysis, the study drug should not be taken until after following their dialysis procedure on days when they receive dialysis. Note that the same requirement for meal timing of study drug must also be followed.

6.4.2 Identity of Investigational Product(s)

6.4.2.1 Formulation of Study Drug

CR845 will be provided as enteric-coated tablets at doses of 0.25, 0.5, and 1 mg. Placebo will also be provided as enteric-coated tablets. All tablets (CR845 and placebo) are white in color with no markings and are identical in appearance, regardless of dose.

6.4.2.2 Packaging, Labeling, and Storage Stability of Study Drug

Study drug must be stored refrigerated. CR845 tablets will be provided in 15-count bottles.

Labeling of the bottles will include but not limited to the following:

- Study protocol number (CR845-210301)
- Bottle number
- Patient identification number
- Temperature storage instructions
- Name and location of Sponsor
- Administer according to protocol
- Caution: New Drug Limited by Federal (or United States) Law to Investigational Use

6.4.3 Drug Accountability

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

The Investigator must confirm receipt of the study drug with his/her signature. A copy of this receipt must be kept by the Investigator and another copy will be stored at Cara

Therapeutics. Until the study drug is dispensed to the patients, it must be stored at 2°C to 8°C in a securely locked area that is not generally accessible.

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

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 1:1:1:1 ratio to receive CR845 0.25 mg, 0.5 mg, 1 mg, or placebo. Randomization will be stratified according to the patient's renal disease status: moderate CKD non-dialysis; severe CKD non-dialysis; severe CKD on dialysis (ie, 3 categories).

6.4.5 Treatment Compliance

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

In addition, patients will be asked to record their daily intake of study drug.

6.4.6 Blinding

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. 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.

6.4.7 Prior, Concomitant, and Prohibited Medications

6.4.7.1 Prior and Concomitant Medications

Prior medications (including vitamins and herbal supplements) are defined as those that the patient has taken any time during the 30 days prior to Screening up until the first dose of study drug on Day 1. Concomitant medications are medications that are taken from after the start of the first dose of study drug on Day 1 of the Treatment Period through the End-of-Treatment/Early Termination Visit. Only medications that are used for adverse events will be recorded from the time after the End-of-Treatment/Early Termination Visit through the Follow-up Visit.

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

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

6.4.7.2 Restricted and Prohibited Medications

During the Treatment Period, 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 light-B treatments	**Not allowed**
Naloxone, naltrexone, or mixed agonist-antagonists (eg, buprenorphine and nalbuphine)	**Not allowed**, unless needed to treat an adverse event or emergent medical condition acutely.
Antihistamines (oral, IV, or topical) Corticosteroids (oral, IV, or topical) treatments Opioids	**Changes to current prescription should be avoided** from 14 days prior to Screening to the end of the Treatment Period unless for the treatment of an adverse event or emergent medical condition.
Gabapentin, pregabalin	No new medication to treat itch should be initiated.

All new concomitant medications or change of frequency and doses of a concomitant medication will be recorded and taken into consideration during the assessment of an adverse event.

6.5 Study Assessments and Procedures

Study procedures are summarized in Table 2 and Table 3.

An informed consent form (ICF) will need to be signed prior to initiation of Screening and any procedures that follow.

Table 2. Schedule of Events

Study Procedures	Screening Period	Run-in Period	Treatment Period						EOT or Early Termination	Follow-up[j]
Study Week			1	2	4	6	8	10	12	
Visit Days	-28 to -7	-7 to -1	1	14	28	42	56	70	84 (or following discontinuation at any time)	7 to 10 days after EOT/Early Termination
				◄ ±2 days ►						
Administrative procedures										
Informed consent	X									
Inclusion/exclusion criteria	X		X							
Medical history	X									
Review drug dosing instructions with patient			X							
Randomization			X							
Safety and efficacy evaluations										
Physical examination	X									
Height	X									
Weight (this is the prescription dry body weight for hemodialysis patients)	X									
12-lead electrocardiogram	X		X[a]						X	
Vital signs[b]	X		X[a]	X	X	X	X	X	X	
Hematology	X		X[a]			X			X	
Serum chemistry	X		X[a]			X			X	
Serum pregnancy (females of childbearing potential only)	X		X[a]						X	
Dispense study drug and drug diary[c]			X	X	X	X	X	X		
Patient training on PRO worksheets		X[d,e]	X[e]							
Worst Itching Intensity NRS (daily)		X	X[f]						X	
Skindex-10, 5-D Itch Scale, Patient Global Impression of Worst Itch Severity[g]			X[a]		X		X	X	X	
Patient Global Impression of Change									X	
Adverse event assessment	◄									►
Prior medications	X									
Concomitant medications[h]			◄							►

CKD = chronic kidney disease; EOT = end of treatment; NRS = numerical rating scale; PRO = patient-reported outcome

Table 2. Schedule of Events (Continued)

a. To be collected/performed prior to the first dose of study drug on Day 1.
b. Vital signs, including body temperature, heart rate, and blood pressure, will be obtained while the patient is in a sitting or semi-recumbent position.
c. Study drug will be dispensed to patients in bottles of 15 tablets following randomization on Day 1 and thereafter at each visit during the Treatment Period until the end of treatment/early termination visit. Patients may be contacted to verify or remind them to take their tablet daily per the protocol. Patients must record when they took the study drug in a drug diary every day during the Treatment Period.
d. Training on Worst Itching Intensity NRS on the first day of the Run-in Period.
e. Training on Skindex-10, 5-D Itch, and Patient Global Impression of Worst Itch Severity may be performed at any time during the Run-in Period or on Day 1 of the Treatment Period.
f. Patients will be requested to complete the NRS worksheets at a similar time each day.
g. Skindex-10, 5-D Itch, and Patient Global Impression of Worst Itch Severity are to be completed at the clinical site.
h. Concomitant medications will be updated at each study visit following the first dose of study drug on Day 1.
j. A phone follow-up will be conducted, unless otherwise necessary.

Table 3. Schedule for Patient-reported Outcome Assessments and Training

	Run-in Period		Treatment Period				
			Treatment Period				EOT or Early Termination
Study Week			1	4	8	10	12
Visit Days	-7	-6 to -1	1	28	56	70	84 (or following discontinuation at any time)
PRO TRAINING							
Worst Itching Intensity NRS	X		Refresher training, as needed.				
Skindex-10 and 5-D Itch worksheets	Any time during the Run-in Period or Day 1		X	Refresher training, as needed			
PRO ADMINISTRATION/RECORDING							
Worth Itching Intensity NRS	X	Worksheet completed daily[a]	Worksheet completed daily[a]				X
Skindex-10, 5-D Itch Scale, Patient Global Impression of Worst Itch Severity[b]			X	X	X	X	X
Patient Global Impression of Change[b]							X

NRS = numerical rating scale; PRO = patient-reported outcome
a. To be completed at home around a similar time of day.
b. To be completed at the clinical site.

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 and the adverse event(s) reported, as well as changes to concomitant medications, as applicable. Additional testing (eg, laboratory tests, vital signs, ECGs) will be performed, as clinically indicated.

6.5.1 Efficacy Assessments

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

- Worst Itching Intensity NRS score
- Skindex-10 Scale
- 5-D Itch Scale
- Patient Global Impression of Change (PGIC)
- Patient Global Impression of Worst Itch Severity

Patients will be trained on completion of the Worst Itching Intensity NRS scale at the first day of the Run-in Period, and will be trained on Skindex-10 Scale, 5-D Itch Scale, Patient Global Impression of Worst Itch Severity, and PGIC worksheets at any time during the Run-In Period or on Day 1 of the Treatment Period. All questionnaires must be completed in strict adherence to the Patient Reported Outcomes Instructions (as per Study Reference Manual).

6.5.1.1 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.

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].

6.5.1.2 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 both itch intensity as well as other instruments evaluating quality of life in patients with uremic pruritus [Mathur 2010]. Patients are asked to fill in 1 of 7 circles numbered from 0 (labeled with the anchor phrase "never bothered") to 6 (labeled as "always bothered") for each of the 10 questions. The total score is the sum of the numeric value of each answered question. The total score is subdivided into 3 domain scores, which are sums of the scores of the following questions: disease domain (questions 1 to 3), mood/emotional distress domain (questions 4 to 6), and social functioning domain (questions 7 to 10).

6.5.1.3 5-D Itch Scale

The 5-D Itch Scale was developed as a brief, but multidimensional questionnaire designed to be useful as an outcome measure in clinical trials. The 5 dimensions of itch assessed are degree, duration, direction, disability, and distribution (Appendix 4, Section 14.4). The scale has been validated in patients with chronic pruritus and has been shown to be sensitive to changes in pruritus over time [Elman 2010].

6.5.1.4 Patient Global Impression of Change

The PGIC is a global PRO measure that assesses the change (improvement or worsening) in overall status relative to the start of the study [Dworkin 2005]. The scale has only 1 item, with values ranging from 1 (Very Much Improved) to 7 (Very Much Worse) (Appendix 5, Section 14.5).

6.5.1.5 Patient Global Impression of Worst Itch Severity

The Patient Global Impression of Worst Itch Severity is a PRO measure that assesses itch severity [Guy 2000]. The scale has only 1 item, with 5 possible values ranging from none to very severe (Appendix 6, Section 14.6).

6.5.2 Safety Assessments

The safety assessments for each patient are the following:

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

6.5.2.1 Adverse Events

6.5.2.1.1 Definition of Adverse Event

An adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and that 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 pre-existing 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 in Section 6.5.2.1.3 will be reported as a serious adverse event (SAE) using the SAE Report Form, in addition to documenting in the eCRF.

6.5.2.1.2 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

6.5.2.1.3 Definition of Serious Adverse Events

An SAE is any untoward medical occurrence that:

- Results in death;
- Is life-threatening;

  NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that 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.

6.5.2.1.4 Severe vs Serious Adverse Event

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

6.5.2.1.5 Adverse Event Causality or Relatedness to the Study Drug

Every effort should be made by the Investigator to explain each adverse event and assess its relationship, if any, to study drug. The Investigator should consider many factors, including, but not limited to, temporal association of the event and date/time of study

drug, duration of study drug, medical/biologic plausibility, pharmacology and adverse event profile of study drug, medical history (past medical history, underlying disease, 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 than to any other possible cause(s). Conversely, an event is considered 'Not Related' if there is reasonable possibility that the event is related to other factors than the study drug.

6.5.2.1.6 Adverse Event Documentation and Follow-up

All adverse events, including observed, elicited, or volunteered problems, complaints, or symptoms are to be recorded on the adverse event page in the patient's eCRF from the time the patient signs the ICF 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, severity, causal relationship to study drug, action taken with study drug, and outcome (resolved, resolved with sequelae, resolving, not resolved, 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 or 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.

6.5.2.1.7 Serious Adverse Event Notification, Documentation, and Reporting

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

Details for reporting and follow-up of SAEs are provided in the Safety Management Plan.

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

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

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

It is the responsibility of Cara Therapeutics to send all regulatory reports to the FDA. Adverse events that are serious, related to the study drug, and unexpected (per the Investigator's Brochure) will be reported to the FDA as per Code of Federal Regulations 21 Code of Federal Regulations (CFR) 312.32 on Investigational New Drug safety reporting and as specified in the Safety Management Plan.

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

As applicable, the Sponsor will also notify other participating Investigator(s) of all Investigational New Drug 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.

6.5.2.2 Physical Examination

Physical examinations at screening will include an examination of the heart, lungs, abdomen, extremities, and neurological and vascular systems. Clinically significant abnormalities will be reported as medical history.

6.5.2.3 Vital Signs

Vital signs include sitting or semi-recumbent body temperature, heart rate, and blood pressure.

Measurements will be repeated if a value is out of the reference range due to a technical issue, considered abnormal for the patient, or for other medical concerns. 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 staff will evaluate and manage the patient per standard practices with knowledge of the patient's typical blood pressure and heart rate excursions.

6.5.2.4 Electrocardiogram

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

6.5.2.5 Clinical Laboratory Tests

Blood samples for clinical laboratory tests, including hematology, serum chemistry and serum pregnancy will be analyzed by the central laboratory. Processing and shipment of central laboratory samples will be described in the Laboratory Manual, along with the final list of laboratory tests.

6.5.2.6 Contraception and Pregnancy

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

- Surgically sterile (ie, tubal ligation, bilateral oophorectomy, and/or hysterectomy); or
- 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 are methods with a failure rate of <1% per year, and include hormonal contraceptives for at least 1 cycle of treatment before study

enrollment, an intrauterine device, and double-barrier method (eg, male or female condom, diaphragm).

Per inclusion criteria, male patients will agree not to donate sperm after the first dose of study drug until 7 days after the last dose 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.

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

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

7.0 Discussion and Justification of Study Design

7.1 Discussion of Study Design and Choice of Control Groups

This is a multicenter, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of oral CR845 in CKD patients with moderate-to-severe pruritus. A randomized, double-blind design was chosen to minimize bias. 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 safety and pharmacokinetic data from Studies CR845-CLIN1301 and CR845-CLIN1303 provided the basis for the selection of the doses and dosing regimen of oral CR845 to be used in this study. In Study CR845-CLIN1301 (Part B) conducted in hemodialysis patients with once-daily oral administration, CR845 was safe and well tolerated at doses of 0.25, 0.5, and 1 mg over a treatment period of 7 days (oral dosing was after the end of dialysis on dialysis days). TEAEs were generally mild to moderate in severity and not dose-related. Two patients experienced serious TEAEs (diabetic foot ulcer in 1 placebo patient and hypertensive encephalopathy in 1 CR845 1 mg patient), neither of which was considered by the Investigator to be related to study drug. There were no deaths and no patient experienced a TEAE that led to premature discontinuation from the study. No clinically important or significant safety findings were observed with respect to laboratory, vital sign, or ECG results.

In Study CR845-CLIN1303 conducted in patients with moderate or severe chronic kidney disease (Stage III, IV, or V, not on maintenance dialysis), once-daily oral administration of CR845 was safe and well tolerated at doses of 0.25, 0.5, and 1 mg over an 8-day treatment period. TEAEs were generally mild to moderate in severity with no treatment-related serious TEAEs reported. There were no deaths and no patient experienced a treatment-related TEAE that led to premature discontinuation from the study. No clinically important or significant safety findings were observed with respect to laboratory, vital sign, or ECG results.

In the Phase 2 Study CR845-CLIN2101, the IV dose of 0.5 mcg/kg of CR845 was established as an effective antipruritic dose in hemodialysis patients with moderate-to-severe pruritus when administered after each dialysis over an 8-week treatment period. Based on the crossover phase of study CR845-CLIN1301, it was determined that a single oral dose of 1 mg produces comparable exposure in hemodialysis patients to an IV dose of 1 mcg/kg. From the pharmacokinetic data with oral dosing established in the studies CR845-CLIN1301 and CR845-CLIN1303, a daily oral dose of CR845 ranging from 0.5 to 1 mg in patients with moderate-to-severe CKD, as well as CKD patients on dialysis, will provide comparable systemic exposure to the 0.5 mcg/kg IV dose established in hemodialysis patients. Therefore, oral doses of 0.25, 0.5, and 1.0 mg were selected to

bracket the exposure anticipated to produce an antipruritic effect in this patient population.

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 (see Sections 6.5.1.1 through 6.5.1.5).

8.0 Statistical Methods

8.1 General Considerations

This protocol describes key safety and efficacy analyses of data collected as currently planned. A SAP will be developed based on the clinical protocol and eCRFs and finalized prior to unblinding of the study; it will include a detailed description of the statistical methodology including the treatment of missing data and the patient eligibility criteria. No database will be locked or analyses completed until the SAP has been approved. If differences occur between analyses of data described in the SAP and the current protocol, those found in the SAP will assume primacy.

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

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

8.2 Determination of Sample Size

The minimum total sample size for this study is N = 240 patients (60 per treatment group) and the maximum is N = 480 (120 per treatment group). An unblinded interim analysis (IA) will be conducted when approximately 50-60% of the planned 240 patients have been randomized and have either completed the 12-week Treatment Period or have discontinued study drug early. The primary goal of the IA is to identify dose(s) of oral CR845 that are both safe and efficacious. Doses that are found to be unsafe or poorly tolerated will be dropped from the study. The sample size of any dose group that is found to be efficacious may be increased to ensure that the pairwise comparison against placebo with respect to the primary efficacy variable at the end of the study is powered appropriately. No dose will be dropped for futility reasons. A sample size of 60 patients per treatment group (the minimum sample size) will provide adequate power (≥80%) for effect sizes ≥0.52 for a 5% type 1 error and a 2-sided T-test. Assuming a standard deviation of 2.6 for the primary efficacy variable, an effect size of 0.52 corresponds to a difference of approximately 1.4 point on a 0- to 10-point scale.

A sample size of 120 patients per treatment group (the maximum sample size) will provide adequate power (≥80%) for effect sizes ≥0.40 for a 5% type 1 error and a 2-sided T-test. Assuming a standard deviation of 2.6 for the primary efficacy variable, an effect size of 0.40 corresponds to a difference of approximately 1 point on a 0- to 10-point scale. The power of a 2-sided hypothesis test with a 5% Type 1 error as a function of sample size and effect size is presented in Table 4.

Table 4. Power as a Function of Effect Size (N = 120 Per Arm)[a]

Effect Size	0.55	0.52	0.50	0.45	0.40	0.35
Power (N = 120)	98%	97%	97%	93%	86%	77%
Power (N = 60)	84%	80%	77%	68%	58%	47%

a. Power for a 2-sided T-test with equal variance 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 1:1:1:1 ratio to receive either placebo or CR845 tablets at doses of 0.25, 0.5, or 1 mg. Randomization will be stratified according to the patient's renal disease status: moderate CKD; severe CKD non-dialysis; severe CKD on dialysis (ie, 3 categories). The randomization of severe CKD patients on hemodialysis will be capped at approximately 20% of the total sample size (ie, 48 of 240 patients).

8.4 Analysis Populations

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

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

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

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

8.5 Statistical Summary and Analysis

8.5.1 Patient Disposition

The number of patients enrolled, treated, who complete the 12-week treatment, or discontinue study drug early, 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.

8.5.2 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.

8.5.3 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->65, 65-<75, ≥75), gender, ethnicity, race, height, prescription dry body weight (kg) (for severe CKD patients on dialysis) or weight (for CKD patients not on dialysis), and body mass index.

Baseline characteristics of the disease will also be summarized overall and by treatment group, and will include variables such as etiology of CKD, renal disease status, years since CKD diagnosis, duration of pruritus, and time on chronic hemodialysis (if applicable).

8.5.4 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 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.

8.5.5 Prior and Concomitant Medications

All medications will be coded using the World Health Organization Drug Dictionary. All prior and concomitant medications (see Section 6.4.7) will be listed and summarized separately by Anatomical Therapeutic Chemical (ATC) class 3, Preferred Term, and treatment group. Additionally, a coding listing will be created which will include all distinct ATC class 3 codes and Preferred Terms along with the corresponding verbatim description of the concomitant medications; sorting will be alphabetically by ATC class 3 and Preferred Term.

8.5.6 Antipruritic Medication

An additional analysis of prior and concomitant antipruritic medications will be conducted. These medications will be summarized by ingredient rather than by ATC codes.

8.6 Efficacy Analyses

8.6.1 Primary Efficacy Endpoint

The primary efficacy endpoint is defined as the change from baseline to Week 12 of the Treatment Period with respect to the weekly mean of the daily 24 hour Worst Itching Intensity NRS score. The weekly mean of the 24-hour Worst Itching Intensity NRS score will be defined as the sum of the daily Worst Itching Intensity NRS score reported during a specific week during the Treatment Period (eg, Days 2 to 8, Days 9 to 15, Days 16 to 22, etc.) divided by the number of days with non-missing scores for that week. If the daily worst itching score is missing for >3 days during a specific week, the corresponding weekly mean worst itching score will be set to missing. The baseline score will be defined as the average of the daily 24-hour Worst Itching Intensity NRS scores over the last 7 days prior to randomization; at least 4 completed Worst Itching Intensity NRS worksheets will be required prior to randomization.

The primary efficacy variable will be analyzed using a mixed effects model with repeated measures (MMRM). The model will contain treatment, week, and treatment-by-week interaction as fixed effects; baseline score and renal disease status as covariates, and patient as a random effect. For each dose group, the treatment group difference vs placebo will be estimated as the simple contrast in the treatment effect at Week 12 of the Treatment Period.

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

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

- 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).
- Results of the MMRM 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, as described below:

- **Sensitivity analysis 1 (missing at random [MAR]):**

In this sensitivity analysis, missing daily worst itching scores will not be imputed. Assuming the data are MAR, the estimates of the treatment differences calculated from the MMRM model described above are unbiased.

- **Sensitivity analysis 2 (Multiple Imputation; MNAR)**

This sensitivity analysis is an implementation of a pattern mixture model that draws from different populations based on the reason for withdrawal. For patients who discontinue study drug due to adverse events, data 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 0 to 10). For patients who discontinue due to reasons other than adverse event, missing data will be imputed using multiple calls of the SAS MI procedure. At each time point, missing data will be imputed using data from patients within each group that have complete data at that time. Results of the MMRM on the multiply imputed data sets will be summarized by the SAS MIANALYZE procedure.

8.6.2 Secondary Efficacy Endpoints

The key secondary efficacy endpoints are the:

- Change from baseline in itch-related quality of life at the end of Week 12, as assessed by the total Skindex-10 Scale score;
- Change from baseline in itch-related quality of life at the end of Week 12, as assessed by the total 5-D Itch Scale score;

- Proportion of patients achieving an improvement from baseline ≥3 points with respect to the weekly mean of the daily 24-hour Worst Itching Intensity NRS score at Week 12 of the Treatment Period.

The Skindex-10 Scale total score and the 5-D Itch Scale total score will be analyzed using MMRM that will contain treatment, week, and treatment-by-week interaction as fixed effects, baseline score and renal disease status as covariates, and patient as a random effect. Repeated measures will include values that reflect the Skindex-10 and 5-D total score at the end of Weeks 4, 8, 10, and 12 (end of treatment). The baseline value will be defined as the value of the Skindex-10 or 5-D total score collected on Day 1 prior to randomization. Missing Skindex-10 Itch Scale and 5-D Itch Scale total scores will not be imputed. The mean treatment difference between CR845 dose and placebo will be estimated as the simple contrast in the treatment effect at Treatment Period Week 12.

An appropriate covariance matrix will be used to model the within-patient errors. The use of an unstructured covariance matrix structure as well as other structures, such as spatial patterns, that require fewer parameters (Toeplitz, autoregressive, or compound symmetry) will be examined. The Akaike information criterion will be used to determine the appropriate covariance matrix for the MMRM. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. The proportion of patients achieving an improvement from baseline ≥3 points with respect to the weekly mean of the daily 24-hour Worst Itching Intensity NRS score at Week 12 of the Treatment Period will be analyzed using logistic regression with terms for treatment group, baseline NRS score, and renal disease status.

Missing NRS data will be imputed using the same methodology described for the primary efficacy endpoint. Specifically,

- 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 derived for the primary efficacy analysis (Section 8.6.1). Differences between each CR845 treatment group and placebo will be compared using a logistic regression model containing terms for treatment group, baseline NRS score and renal disease status.
- Results of the logistic regression on the multiply imputed data sets will be summarized by the SAS MIANALYZE procedure.

8.6.3 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 is rejected in favor of the alternative that patients randomized to CR845 experience significantly less itching as measured by the change from baseline to Week 12 of the Treatment Period with respect to the weekly mean of the 24-hour Worst Itching

Intensity NRS score. This is a Phase 2 study designed to identify a safe and efficacious dose; therefore, each CR845 dose group will be compared against placebo. There will be no adjustment for multiple comparison.

8.6.4 Additional Efficacy Endpoints

8.6.4.1 Itch-intensity Measures

Itch-intensity measures and their analyses will include:

- Proportion of patients who have an improvement from baseline at Week 12 of the Treatment Period with respect to the weekly mean of the 24-hour Worst Itching Intensity NRS scores ≥1, ≥2, and ≥4 points. The calculation of the proportions will be based on the NRS data using an MI approach for the missing data as in the primary efficacy analysis. Treatment differences will be compared using a logistic regression model with terms for treatment group, baseline NRS score and renal disease status.
- A figure presenting the proportion of patients who have an improvement from baseline in NRS scores at Week 12 that are ≥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 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 8.6.1.
- Proportion of patients who rate their itch condition as "Very much improved" or "Much improved" at the end of Week 12 of the Treatment Period/end of treatment, as measured by the PGIC. 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).
- The number and percentage of patients in each of the 5 categories of the Patient Global Impression of Worst Itch Severity at baseline and at each week of the Treatment Period will be tabulated. In addition, the proportion of patients who have a 1-point improvement or more at each week of the Treatment Period, as measured by the Patient Global Impression of Worst Itch Severity. Pairwise treatment differences with respect to this variable will be tested using the Fisher's exact test.

8.6.4.2 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 Treatment Period, as assessed by the total score of the 5-D Itch Scale. Treatment differences

between each CR845 dose group 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 Treatment Period, as assessed by the total score of the Skindex-10 Scale. Treatment differences between each CR845 dose group 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 Treatment Period and at each of the remaining weeks of the 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 total score of the Skindex-10 Scale.
- Change from baseline in itch-related quality of life at Week 12 of the Treatment Period and at each of the remaining weeks of the Treatment Period with respect to each of the domains of 5-D Itch 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 total score of the 5-D Scale.

8.7 Safety Analyses

Analysis of all safety data will be performed using the Safety Population. Safety data will be summarized descriptively. No inferential statistics are planned. The baseline value for all analyses of safety parameters will be defined as the last value obtained prior to the first dose of study drug and will include both scheduled and repeat (unscheduled) observations.

8.7.1 Exposure to Study Drug and Compliance

For this study, the duration of treatment for each individual patient may be up to 12 weeks, for a total of 84 doses of study drug. Day 1 of the Treatment Period will be defined as the day of administration of the first dose of study drug. The last day of the Treatment Period will be defined as the day of the last dose taken by the patient (determined based on the patient daily dosing diary). For all patients, the last day of study will be defined as the date of the Follow-up Visit.

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

- Duration of treatment (days)
- Duration of study (days)

- Total number of doses received (based on the patient daily dosing diary)
- Total number of missed doses (0, 1, ≥2) (based on the patient daily dosing diary)
- Percent compliance (<80%, 80% to 110%, >110%). Compliance will be calculated in 2 different ways: based on the patient daily dosing diary and using drug accountability records

8.7.2 Adverse Events

All adverse events will be coded using MedDRA dictionary to the corresponding 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.

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 Treatment Period.

Adverse events that are considered "treatment emergent" relative to the Treatment Period are identified as any adverse event with an onset date after the first dose of the study drug up to the study End of Treatment/Early Termination Visit (or 7 to 10 days after the last dose if no End of Treatment/Early Termination Visit was conducted), whichever is later.

Treatment-emergent adverse events will be summarized by treatment group and by period (Run-in Period vs Treatment Period). The incidence of TEAEs will be presented using counts and percentages of patients with adverse events and tabulated by SOC and Preferred Term. System Organ Class will be sorted alphabetically and Preferred Term within SOC will be sorted by descending frequency based on the incidence across patients overall. 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 following specific summary tables will be generated:

- Incidence of TEAEs
- Incidence of TEAEs related to study drug
    - If the 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 "related" to the study drug). If a patient reports 2 or more adverse events that code to the same Preferred Term, the event with the maximum relationship will be included in the table.
- Incidence of TEAEs by maximum severity

- If the severity 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"). If a patient reports 2 or more adverse events that code to the same Preferred Term, the event with the maximum severity will be included in the table.

- Incidence of TEAEs occurring in ≥5% of patients in at least 1 treatment group
- Incidence of treatment-related TEAEs occurring in ≥5% of patients in at least 1 treatment group
- Incidence of serious TEAEs
- Incidence of TEAEs leading to study drug discontinuation

In addition, 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), 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.

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 drug, action taken with study drug, 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.

8.7.3 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 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.

8.7.4 Vital Signs and Electrocardiograms

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 prior to the first dose of study drug. If 2 or more evaluations occur in the same visit window, the evaluation closest to the target visit day will be selected for inclusion in the analysis. If multiple evaluations are equally close to the target visit day, the latest evaluation will be selected for inclusion in the analysis.

All vital signs will be listed in 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.

9.0 Quality Control and Quality Assurance

9.1 Study Monitoring Plan

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

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

Name and contact information for monitors will be included in the Investigator Site File.

Clinical laboratory testing will be completed at a central laboratory. The central laboratory will provide a separate manual.

9.2 Audits and Inspections

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

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

9.3 Data Collection, Validation, and Analysis

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

10.0 Ethics and Regulatory Compliance

10.1 Independent Ethics Committee or Institutional Review Board

A properly constituted, valid IRB or Independent Ethics Committee must review and approve the protocol, the Investigator's 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 will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of the patients. The study will only be conducted at a site where IRB approval has been obtained. The protocol, Investigator's Brochure, ICF, advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the Investigator.

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

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

10.2 Ethical Conduct of the Study

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki and all accepted amendments, the ICH principles of GCP (including archiving of essential study documents), and the applicable regulations of the country in which the study is conducted.

The Investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol, 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. In obtaining and documenting informed consent, the Investigator must comply with applicable regulatory requirements and must adhere to GCP regulations. It is the responsibility of the Investigator to ensure that written informed consent is obtained from the patient before any activity or procedure is undertaken that is not part of routine care.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and that continues throughout the individual's study participation. The Investigator or designee will discuss extensively with the participant patient the study risks. Copies of the current, IRB-approved ICF detailing the risks and benefits of study participation will be provided to the participants. Consent forms describing in detail the study drug and study procedures/intervention and risks will be fully explained to the patient and written documentation of informed consent will be required prior to starting participation in the study. Upon reviewing the document, the Investigator or designee will explain the research study to the participant and answer any questions that may arise. The participants will sign the ICF prior to any procedures being done specifically for the study. The participants should have sufficient opportunity to discuss the study and process the information in the consent process prior to agreeing to participate. The participants may withdraw consent at any time throughout the course of the study. A signed copy of the ICF will be given to the participants for their records.

10.4 Patient Confidentiality

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

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

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

The study monitors 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/Independent Ethics Committee review, and regulatory agency inspections and provide direct access to source data documents.

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

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

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

12.0 Administrative Procedures

12.1 Protocol Adherence

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

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

12.2 Publication of Study Findings

All information regarding CR845 provided by Cara Therapeutics to the Investigator is privileged and confidential information. By conducting this study, the Investigator affirms to the Sponsor that he/she will maintain, in strict confidence, information furnished by the Sponsor, including data generated from this study, except as exempted for regulatory purposes. All data generated during the conduct of this study are owned by Cara Therapeutics. The Investigator agrees to use the information to conduct the study and will not use it for other purposes without written permission from Cara Therapeutics. Partial or full data or results from this study cannot be published without express written consent from Cara Therapeutics. It is understood that there is an obligation to provide Cara Therapeutics with complete data obtained during the study. The information obtained from the clinical study will be used toward the development of CR845 and may be disclosed to a 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

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

INSTRUCTIONS

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

Worst Itching Over the Past 24 Hours

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

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

NO ITCHING — **WORST ITCHING IMAGINABLE**

Date Completed: ☐☐ ☐☐☐ 2 0 ☐☐ (D D M M M Y Y Y Y)

Time: ☐☐ : ☐☐ ☐ AM ☐ PM

SUBJECT INITIALS (*First Middle Last*) ☐☐☐

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 Appendix 6: Patient Global Impression of Worst Itch Severity

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.

Please indicate the severity of the **WORST ITCHING** you experienced over the past 24 hours by marking the box with the category that best describes it.

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

Date Completed:

D	D	M	M	M	2	0	Y	Y

Time: ☐☐ : ☐☐ ☐ AM ☐ PM

SUBJECT INITIALS

First	*Middle*	*Last*