# AN OPEN LABEL, MULTICENTER STUDY TO EVALUATE THE SAFETY AND EFFECTIVENESS OF INTRAVENOUS CR845 IN HEMODIALYSIS PATIENTS WITH MODERATE-TO-SEVERE PRURITUS

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| Protocol number: | CR845-CLIN3105 |
| Phase: | 3 |
| IND number: | 123140 |
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| Protocol version: | Version 2.0 |
| Date: | Feb 12, 2019 |
| Sponsor: | Cara Therapeutics, Inc.<br>4 Stamford Plaza<br>Stamford, CT 06902<br>(203) 406-3700 |

## SPONSOR APPROVAL / SIGNATURE PAGE

## INVESTIGATOR APPROVAL STATEMENT

I have read and understand the protocol (CR845-CLIN3105) 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 Harmonization Harmonized Tripartite Guideline for Good Clinical Practice and all applicable regulatory requirements.

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

Printed Name: _____

Signature: _____

Date: _____

# 1.0 Protocol Synopsis

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| STUDY TITLE | An Open-Label, Multicenter Study to Evaluate the Safety and Effectiveness of Intravenous CR845 in Hemodialysis Patients with Moderate-to-Severe Pruritus |
| PROTOCOL NUMBER | CR845-CLIN3105 |
| PHASE OF DEVELOPMENT | 3 |
| INVESTIGATIONAL PRODUCT | CR845 Solution (For Clinical Trial Use Only) |
| NAME OF ACTIVE INGREDIENT | CR845 |
| ROUTE OF ADMINISTRATION | Intravenous (IV) |
| STUDY CENTERS | Approximately 80 US and non-US sites |
| OBJECTIVES | Primary Objective<br>• To evaluate the safety of IV CR845 at a dose of 0.5 mcg/kg in hemodialysis patients with moderate-to-severe pruritus<br>Secondary Objectives<br>• To evaluate the effectiveness of IV CR845 at a dose of 0.5 mcg/kg in reducing the intensity of itch in hemodialysis patients with moderate-to-severe pruritus<br>• To evaluate the effectiveness of IV CR845 at a dose of 0.5 mcg/kg in improving itch-related quality-of-life and quality of sleep measures in hemodialysis patients with moderate-to-severe pruritus. |
| NUMBER OF PATIENTS | Approximately 400 male and female hemodialysis patients with moderate-to-severe pruritus |
| STUDY POPULATION | **Inclusion Criteria:**<br>To be eligible for inclusion into the study, a patient must meet the following criteria:<br>1. Willing and able to provide written informed consent prior to participating in this study;<br>2. Able to communicate clearly with the Investigator and staff, able to understand the study procedures, and able and willing to comply with the study requirements, including providing written responses to questionnaires;<br>3. Male or female between 18 and 85 years of age, inclusive;<br>4. Has end-stage renal disease (ESRD) and has been on hemodialysis 3 times per week for at least 3 months prior to the start of screening;<br>**Note 1**: Patients who require an occasional additional dialysis treatment to manage fluid overload or electrolyte excesses |

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| | may be enrolled as long as it is anticipated that no more than 1 such treatment will be required in any given week. Patients routinely on 4 dialyses a week will not be eligible.<br>**Note 2**: Patients receiving in-home hemodialysis may participate as long as they have switched to in-center hemodialysis at least 2 weeks prior to screening and plan to remain on in-center hemodialysis for the duration of the study.<br>**Note 3**: Patients receiving alternate dialysis modalities such as nocturnal dialysis will not be eligible.<br>5. If female, is not pregnant or nursing during any period of the study;<br>6. If female:<br>a. Is surgically sterile; or<br>b. Has been amenorrhoeic for at least 1 year and is over the age of 55 years; or<br>c. Has a negative serum pregnancy test within 7 days of administration of the first dose of study drug and agrees to use acceptable contraceptive measures (eg, hormonal contraceptives, barrier with spermicide, intrauterine device, vasectomized partner, or abstinence from heterosexual intercourse) from the time of informed consent until 7 days after the last dose of study drug;<br>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;<br>**Note:** No restrictions are required for a vasectomized male provided his vasectomy was performed ≥4 months prior to screening.<br>8. Has a prescription dry body weight ≥40 kg;<br>9. Over the last three months prior to screening, has had at least one of the following:<br>a. At least 2 single-pool Kt/V measurements ≥1.2 on different dialysis days;<br>b. At least 2 urea reduction ratio measurements ≥65% on different dialysis days;<br>c. 1 single-pool Kt/V measurement ≥1.2 and 1 urea reduction ratio measurement ≥65% on different dialysis days;<br>10. Prior to treatment:<br>a. Has completed at least three Worst Itching Intensity Numerical Rating Scale (NRS) questionnaires from the |

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| | start of the Run-in Period up to and including the pre-dose assessment on Day 1;<br>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 Run-in Period up to and including the pre-dose assessment on Day 1.<br>**Exclusion Criteria:**<br>A patient will be excluded from the study if any of the following criteria are met:<br>1. Known noncompliance with dialysis treatment that in the opinion of the Investigator would impede completion or validity of the study;<br>2. Scheduled to receive a kidney transplant during the study;<br>3. Known history of allergic reaction to opiates, such as hives;<br>**Note:** side effects related to the use of opioids, such as constipation or nausea, would not exclude patients from the study.<br>4. Hypersensitivity to the active substance or any of the excipients in the investigational products;<br>5. Has a concomitant disease or a history of any medical condition that, in the opinion of the Investigator, could pose undue risk to the patient, impede completion of the study procedures, or would compromise the validity of the study measurements, including, but not limited to:<br>a. Known or suspected history of alcohol, narcotic, or other drug abuse, or substance dependence within 12 months prior to screening;<br>b. Significant systolic or diastolic heart failure (eg, New York Heart Association Class IV congestive heart failure [Appendix 1, Section 14.1]);<br>c. Severe mental illness or cognitive impairment (eg, dementia);<br>d. Any other relevant acute or chronic medical or neuropsychiatric condition within 3 months prior to screening (eg, diagnosis of encephalopathy, coma, delirium);<br>6. New or change of treatment received for itch including antihistamines and corticosteroids (oral, IV, or topical) within 14 days prior to screening;<br>7. New or change of prescription for opioids, gabapentin, or pregabalin within 14 days prior to screening;<br>8. Received another investigational drug within 30 days or five half-lives (whichever is longer) prior to the start of dosing or is planning to participate in another interventional clinical study while enrolled in this study; |

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| | 9. In the opinion of the Investigator, has pruritus attributed to a cause other than ESRD or its complications (eg, patients with concomitant pruritic dermatological disease or cholestatic liver disease);<br>**Note**: Patients whose pruritus is attributed to ESRD complications, such as hyperparathyroidism, hyperphosphatemia, anemia, or the dialysis procedure or prescription may be enrolled.<br>10. Has localized itch restricted to the palms of the hands;<br>11. Has pruritus only during the dialysis session (by patient report);<br>12. Is receiving ongoing ultraviolet B treatment and/or anticipates receiving such treatment during the study;<br>13. Participated in a previous clinical study with CR845. |
| STUDY DESIGN | This is a multicenter, open-label study to evaluate the safety and effectiveness of IV CR845 at a dose of 0.5 mcg/kg administered after each dialysis session. This study will consist of a Screening Period and an up to 12-week Treatment Period. The Screening Period includes a Screening Visit and a Run-In Period. After the completion of the Treatment Period, patients will be required to complete a Follow-up Visit.<br>**Screening Period**<br>***Screening Visit:***<br>Informed consent will be obtained prior to performing any study-specific procedures. The Screening Visit will occur within 21 days prior to the start of the Run-in Period. Patients should be trained on completing patient-reported outcome (PRO) questionnaires prior to the start of the Run-in Period. The site has the option of starting the Run-in Period on the same day as the Screening Visit at the discretion of the Investigator.<br>***Run-In Period:***<br>Patients will start the Run-in Period during the week prior to Treatment Period to complete eligibility verification. The Run-in Period will start on the first dialysis session of that week (i.e, Monday for patients on a Monday-Wednesday-Friday dialysis schedule or Tuesday for patients on a Tuesday-Thursday-Saturday dialysis schedule). The primary purpose of the Run-in Period is to confirm that each patient has moderate-to-severe pruritus (ie, weekly average worst itching score $\geq$5), as measured by the patient reported Worst Itching Intensity NRS and to establish a baseline itch intensity. During the Run-in Period, patients will complete the Worst Itching Intensity NRS and Sleep Quality questionnaires only on the dialysis days and the EQ-5D-5L with EQ-PSO bolt on (EQ-5D-5L-P) on the third dialysis session. |

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| | If patients continue to meet all inclusion criteria and none of the exclusion criteria by the end of the Run-in Period, they will enter the Treatment Period of the study.<br>**Treatment Period:** Day 1 of the Treatment Period will be defined as the day of administration of the first dose of study drug and will occur on the first dialysis session of the first treatment week (ie, Monday for patients on a Monday-Wednesday-Friday dialysis schedule, or Tuesday for patients on a Tuesday-Thursday-Saturday dialysis schedule).<br>Before the first dose of CR845, patients will complete their Worst Itching Intensity NRS and a series of itch-related quality of life and sleep questionnaires (ie, Sleep Quality, 5D Itch, Skindex-10, and EQ-5D-5L-P questionnaires).<br>All scheduled study visits during the Treatment Period will be conducted on dialysis days. Patients will be administered CR845 as an IV bolus after the end of their dialysis, either during rinse back or after rinse back. Hospitalizations, infections, missed dialysis sessions, clinical laboratory tests, electrocardiograms (ECGs), vital signs, adverse events, and concomitant medications will be monitored throughout the study.<br>End of treatment (EOT) is defined as the first day of dialysis following the last dose of drug. The EOT procedures will be conducted on the dialysis visit following the last dose of study drug.<br>**Follow-up Visit**<br>A final safety Follow-up Visit will be conducted 7-10 days after the EOT or Early Termination (ET) Visit. |
| STUDY DRUG | Study drug will be supplied in glass vials containing an extractable volume of at least 1.3 mL of CR845 at a concentration of 0.05 mg/mL in 0.04M isotonic acetate buffer, pH 4.5. CR845 dose will be calculated and adjusted based on prescription dry body weight. |
| REFERENCE PRODUCT | No placebo will be used for this study. |
| TREATMENT REGIMENS | Patients will be administered 0.5 mcg/kg CR845 as a single IV bolus 3 times a week after each dialysis session for up to 12 weeks. |
| STUDY DURATION | Screening Period:<br>Screening Visit: up to 21 days prior to Run-In<br>Run-In Period: 7 days prior to Treatment Period<br>Treatment Period: up to 12 weeks<br>End of Treatment Visit: First day of Week 13 or at Early Termination<br>Follow-up Visit: 7-10 days after the EOT Visit or ET Visit<br>Total study duration for a single patient: up to 18 weeks |
| STUDY ENDPOINTS | **Safety Endpoints**<br>• Adverse events<br>• ECG |

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| | • Vital signs<br>• Clinical laboratory values<br><br>**Effectiveness Endpoints**<br><br>• Worst Itching Intensity NRS<br>• Sleep Quality<br>• 5D-Itch<br>• Skindex-10<br>• EQ-5D-5L-P<br><br>**Additional Endpoints**<br><br>• Missed dialysis visits<br>• Hospitalizations<br>• Incidence of infections |
| STATISTICAL ANALYSIS | Enrolled population is defined as the group of patients who sign informed consent.<br><br>Safety population is defined as the group of patients who received at least 1 dose of CR845 in the study.<br><br>Full Analysis population is defined as the group of patients who received at least 1 dose of CR845 and have least one non-missing effective endpoint assessment after baseline.<br><br>All summaries and analysis of safety will be conducted using the Safety population.<br><br>Effectiveness endpoints analysis will be conducted using the Full Analysis population.<br><br>Safety data will be summarized descriptively. No inferential statistics are planned. Analyses of safety data will include summaries of treatment-emergent adverse events including Adverse Events of Special Interest (AESI), serious adverse events, and adverse events resulting in study drug discontinuation. Vital signs, chemistry and hematology, ECG data will be presented by visit as applicable, in addition to change from baseline. |

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# 3.0 List of Abbreviations

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| AESI | Adverse Event of Special Interest |
| ATC | Anatomical Therapeutic Chemical |
| CFR | Code of Federal Regulations |
| CKD | Chronic Kidney Disease |
| CKD-aP | Chronic Kidney Disease-associated Pruritus |
| CI | Confidence Interval |
| CNS | Central Nervous System |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| ESRD | End-Stage Renal Disease |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| H | Above the Laboratory Parameter's Reference Range |
| ICF | Informed Consent Form |
| ICH | International Council for Harmonization |
| IEC | Independent Ethics Committee |
| IND | Investigational New Drug |
| IRB | Institutional Review Board |
| ISF | Investigator Site File |
| IV | Intravenous |
| KOR | Kappa-Opioid Receptor |
| L | Below the Laboratory Parameter's Reference Range |
| LS | Least Squares |
| 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 |
| PRO | Patient-Reported Outcome |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SE | Standard Error |
| SOC | System Organ Class |
| TEAE | Treatment-Emergent Adverse Event |
| ULN | Upper Limit of Normal |

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

# 4.0 Introduction

## 4.1 Background and Rationale

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

Opioid receptors are involved in the modulation of itch and pain signals and consist of 3 subtypes: mu, kappa, and delta. These receptor subtypes are found in the central nervous system (CNS), in peripheral nervous system tissues, such as skin and viscera, and in the immune system (see Investigator's Brochure for references and further details). CR845 was designed to only activate KORs located outside of the central nervous system, to avoid producing the side effects associated with the activation of mu-opioid receptors, such as respiratory depression, addiction, and constipation.

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

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

Although the pathophysiology of moderate-to-severe pruritus in hemodialysis patients is not well understood, there is increasing evidence that it is likely multifactorial and that an immune system dysfunction (including elevated proinflammatory activity) and imbalance in the endogenous opioid system (with over-expression of mu-opioid receptors in dermal cells and lymphocytes and concomitant downregulation of KORs) are involved [Kimmel 2006; Narita 2006; Phan 2012; Patel 2007; Mettang 2002; Tey 2011].

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

## 4.2 Clinical Experience

### 4.2.1 Overall Exposure

As of October 2018, the intravenous (IV) formulation of CR845 has been evaluated in >1440 patients and healthy volunteers across 17 studies (including two Phase 2 studies for the relief of moderate-to-severe pruritus and an ongoing long-term safety trials in hemodialysis patients conducted in the US). CR845 has been evaluated both as an IV bolus and a 15-minute infusion of single or repeated doses ranging from 0.25 to 40 mcg/kg.

Of the patients exposed to IV CR845 to date, >450 hemodialysis patients have received single or repeated IV injections of CR845 doses (for up to 1 year) ranging from 0.25 to 6 mcg/kg across Phase 1 to Phase 3 studies with > 90 and > 30 hemodialysis patients exposed to the intended therapeutic dose of 0.5 mcg/kg for 6 months and for one year, respectively.

### 4.2.2 Safety in Hemodialysis Patients

A review of the aggregate safety data in completed Phase 1 and Phase 2 trials shows that CR845 was generally well tolerated in hemodialysis patients when administered after each dialysis session for up to 8 weeks at IV doses ranging from 0.5 mcg/kg to 6 mcg/kg. Although patients exposed to CR845 reported more adverse events compared with placebo patients, most events were mild or moderate in nature. Generally mild, transient paresthesias (facial tingling) and/or hypoesthesias (in different anatomic locations), mostly on the first week of dosing, as well as headache, dizziness, and somnolence, were the most frequently reported adverse events associated with CR845 administration. Consistent with its lack of affinity for mu-opioid receptors, CR845 did not cause euphoria or respiratory depression.

The study CR845-CLIN2101 evaluated the safety, pharmacokinetics, and efficacy of repeated IV doses of CR845 compared to placebo over an 8-week treatment period in 174 hemodialysis patients. As expected with patients on hemodialysis, a significant number of the reported serious adverse events (SAEs) were considered not treatment-related, but related to the disease and/or comorbid conditions. Of the 174 patients randomized and treated on the study, 31 (17.8%) had treatment-emergent SAEs. Out of these SAE reports, 4 (9%) occurred in 45 placebo-treated patients and 27 (21%) in 129 CR845-treated patients. Only 1 SAE of mental status changes (moderate in severity) in a patient who received CR845 1.5 mcg/kg IV was considered by the Investigator to be probably related to study drug. However, based on the Sponsor's medical review, an alternate etiology of urgent/emergent hypertension offers a more plausible explanation for the acute change in mental status. There were 4 patient deaths (1 in placebo group, 1 in

CR845 0.5 mcg/kg group, and 2 in CR845 1.5 mcg/kg group; 2.3% of the total study population) in the study, all of which were considered not related to the study drug. In patients with normal renal function, CR845 can cause free-water diuresis (aquaresis) and increased serum sodium. However, as would be expected in patients undergoing dialysis in whom there are few functioning nephrons, there was no evidence of aquaresis or significant increases in serum sodium concentrations. There were no adverse trends in clinical chemistry or hematology values (drawn pre-dialysis), including no apparent differences between the placebo and CR845 groups in serum sodium. There were no discernable differences between treatment groups in vital sign results. Of particular note, among patients receiving CR845, there was no apparent reduction in blood pressure or respiratory rate following dosing.

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

### 4.2.3 Efficacy of CR845 in Hemodialysis Patients with Uremic Pruritus

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

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

CR845-CLIN2101 evaluated the safety, pharmacokinetics, and efficacy of repeated IV doses of CR845 compared to placebo over an 8-week treatment period in 174 hemodialysis patients experiencing moderate-to-severe pruritus daily or near-daily for 4.4 years on average. The study was conducted at 33 dialysis centers and assessed the effect of 3 doses of CR845 (ie, 0.5 mcg/kg, n=44; 1 mcg/kg, n=41 and 1.5 mcg/kg, n=44) or placebo (n=45) administered at the end of each dialysis session (ie, 3 times/week). The primary efficacy endpoint for Study CR845-CLIN2101 was based on itch intensity measurement and defined as the change from a 1-week baseline recorded prior to the start of study drug to the last week of the 8-week treatment period with respect to the weekly mean of the daily 24-hour Worst Itching Intensity numerical rating scale (NRS) score. The least squares (LS) mean (±standard error [SE]) treatment group difference from placebo at Week 8 across all CR845 doses was -1.3 (±0.41) (95% confidence interval [CI]: -2.1 to -0.5) (p=0.002) with an average NRS score reduction from baseline of -3.2 (±0.22) (LS mean ±SE) and 95% CI ranging from -3.7 to -2.8. Examination of the individual

CR845 dose group results for the Full Analysis Population indicates that a substantial improvement over placebo was observed with all 3 doses. These differences from placebo were statistically significant for the lower dose group of 0.5 mcg/kg ($p<0.001$) and the 1.5 mcg/kg group ($p=0.019$), with an effect size estimated as 0.82, 0.39, and 0.62 for the 0.5, 1.0, and 1.5 mcg/kg doses, respectively. Average reduction from baseline (LS mean ± SE) ranged from -2.8 (±0.38) in the 1.0 mcg/kg dose group (95% CI ranging from -3.5 to -2.0) to -3.8 (±0.38) in the 0.5 mcg/kg dose group (95% CI ranging from -4.5 to -3.1). The reduction in itch intensity directly correlated with a significant improvement in itch-related quality of life and sleep measurements (see Investigator's Brochure, with further details of the efficacy profile of CR845).

### 4.2.4 Pharmacokinetics in Hemodialysis Patients

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

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

## 4.3 Summary of Potential Risks and Benefits

During preclinical development, no specific safety findings to preclude the use of CR845 in humans were observed. During early clinical development, IV CR845 was administered to healthy volunteers; patients with mild, moderate, or severe renal impairment, including end-stage renal disease (ESRD) and hemodialysis patients; recreational poly-drug users; and postsurgical patients. The effects of CR845 have been shown to be in line with the underlying pharmacological mechanism of KOR activity. Consistent with the nonclinical abuse liability studies conducted to date, the results of an abuse-potential study in humans indicated that CR845 is different from typical opioid medications as it does not attach to the mu receptors and therefore cannot produce mu receptor mediated side-effects such as addiction.

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

# 5.0 Objectives

**Primary Objective**

- To evaluate the safety of IV CR845 at a dose of 0.5 mcg/kg in hemodialysis patients with moderate-to-severe pruritus

**Secondary Objectives**

- To evaluate the effectiveness of IV CR845 at a dose of 0.5 mcg/kg in reducing the intensity of itch in hemodialysis patients with moderate-to-severe pruritus
- To evaluate the effectiveness of IV CR845 at a dose of 0.5 mcg/kg in improving itch-related quality-of-life and quality of sleep measures in hemodialysis patients with moderate-to-severe pruritus.

# 6.0 Investigational Plan

## 6.1 Overall Study Design and Plan: Description

This is a multicenter, open-label study to evaluate the safety and effectiveness of IV CR845 at a dose of 0.5 mcg/kg administered after each dialysis session. This study will consist of a Screening Period, an up to 12-week Treatment Period and a Follow Up Visit.

### 6.1.1 Screening Period

The Screening Period can occur within 28 days prior to treatment to assess eligibility. It consists of a Screening Visit and a Run-in Period.

#### 6.1.1.1 Screening Visit

The Screening Visit will occur within 21 days prior to the Run-In Period. During this visit, patients will sign the Informed Consent Form and then will be evaluated for eligibility by assessment of inclusion/exclusion criteria.

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

Medical history, including total number of missed dialysis sessions over the past month and the conditions of special interest (ie, gait disturbance, fall, dizziness, somnolence, seizure, syncope, mental status changes, mood altered, feeling abnormal, tachycardia, and palpitations) will be recorded during screening. During screening and before the first visit of the Run-in Period, patients will be trained on completion of the Worst Itching Intensity NRS, EQ-5D-5L with EQ-PSO bolt-on (EQ-5D-5L-P) and Sleep Quality questionnaires. Patients may also be trained on other patient-reported outcome (PRO) questionnaires during the Screening Period prior to treatment on Day 1 (ie, Skindex-10 and 5-D itch questionnaires).

#### 6.1.1.2 Run-in Period

Eligible patients will begin the Run-in Period during the week prior to Treatment Period to complete eligibility verification, starting on the first dialysis session of that week (ie, Monday for patients on a Monday-Wednesday-Friday dialysis schedule or Tuesday for patients on a Tuesday-Thursday-Saturday dialysis schedule). The purpose of the Run-in Period will be to confirm that each patient has moderate-to-severe pruritus (ie, weekly average worst itching score $\geq$5), as measured by the patient reported Worst Itching Intensity NRS, and to establish a baseline itch intensity. These criteria for eligibility should not be communicated to the patients. This period will also be used to record each patient's use of antipruritic medications.

During the first dialysis visit of the Run-in Period, patients will start the reporting of their Worst Itching Intensity NRS scores and will continue to do so at every dialysis session. For consistency the Worst Itching Intensity NRS scores will be collected at approximately the same time around the start of the dialysis session preferably within one hour of starting

dialysis. After the completion of the Worst Itching Intensity NRS, patients will complete the Sleep Quality Questionnaire. On the third dialysis session of the Run-in Period (Friday or Saturday), patients will complete the EQ-5D-5L-P questionnaire. Preferably, the patients will complete the sleep questionnaire followed by the EQ-5D-5L and then the EQ-PSO bolt on. Patients may continue to be trained on PRO questionnaires during the Run-in Period.

The site has the option of starting the Run-in Period on the same day as the Screening Visit at the discretion of the Investigator. In these cases, all screening procedures should be conducted first, and then Run-in procedures should be conducted after confirmation of eligibility with exception of the lab results, which will be reviewed during the Run-in Period.

#### 6.1.1.3 Treatment Period

If patients continue to meet all inclusion and no exclusion criteria at the end of the Run-in Period, they will be able to start the Treatment Period and begin IV CR845 0.5 mcg/kg.

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

All scheduled study visits during the Treatment Period will be conducted on dialysis days. Patients will be administered CR845 as an IV bolus after the end of their dialysis, either during rinse back or after rinse back, during a Treatment Period of up to 12-week so that each patient will receive CR845 3 times weekly for a total of up to 36 doses.

On Day 1, before the first dose of CR845, patients will complete the Worst Itching Intensity NRS, Sleep Quality, 5-D Itch, and Skindex-10 questionnaires.

The Worst Itching Intensity NRS and Sleep Quality will also be completed at each dialysis session (Monday/Wednesday/Friday or Tuesday/Thursday/Saturday) during Week 12. In addition, the EQ-5D-5L-P questionnaire should be performed during the third dialysis session (Friday/Saturday) of Week 12.

At the End of Treatment visit (the first dialysis session after last dose of CR845), patients will complete the Worst Itching Intensity NRS, Sleep Quality, 5-D Itch, and Skindex-10 questionnaires preferably within one hour of starting dialysis.

All questionnaires will be performed at Early Termination.

On days when multiple questionnaires are to be completed, the following sequence should be adhered to:

1. Itching Intensity NRS questionnaire
2. Sleep Quality questionnaire
3. 5-D Itch
4. Skindex-10

5. EQ-5D-5L-P

All questionnaires are to be completed preferably within one hour of starting dialysis but before the completion of dialysis.

Clinical laboratory tests (see detail in Section 6.5.3.5) will be collected during first day of treatment and at End of Treatment or Early Termination Visit. Pre-dialysis vital signs will be monitored and recorded on the third dialysis session of the week for Week 1 and every four weeks after Week 1. Adverse events, infection assessment, and concomitant medications will be continuously recorded during the Treatment Period. Electrocardiograms (ECGs) will be monitored at the Screening Visit and at End of Treatment or Early Termination Visit.

The number and reason(s) for missed dialysis, hospitalizations (including duration) and the use of antipruritic medications will be recorded throughout the study.

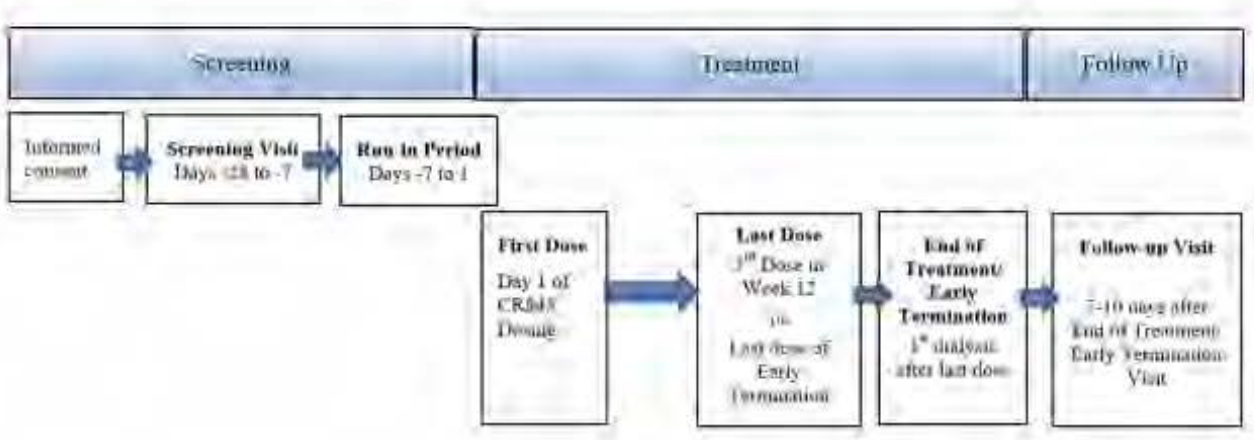
End of Treatment or Early Termination is defined as the first dialysis day following the last dose of study drug.

#### 6.1.1.4 Follow-up Visit

Patients will have a final safety Follow-up Visit conducted 7-10 days after the Early Termination or End of Treatment Visit.

The study schematic is shown in Figure 1.

**Figure 1. CR845-CLIN3105 Study Schematic**



## 6.2 Selection of Study Population

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

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

Patients providing informed consent will be screened for inclusion in the study. All eligibility criteria must be met before a patient receives the first dose of study medication.

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

### 6.2.1 Eligibility 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, including providing written responses to questionnaires;
3. Male or female between 18 and 85 years of age;
4. Has end-stage renal disease (ESRD) and has been on hemodialysis 3 times per week for at least 3 months prior to the start of screening;

   **Note 1**: Patients who require an occasional additional dialysis treatment to manage fluid overload or electrolyte excesses may be enrolled as long as it is anticipated that no more than 1 such treatment will be required in any given week. Patients routinely on 4 dialyses a week will not be eligible.

   **Note 2**: Patients receiving in-home hemodialysis may participate as long as they have switched to in-center hemodialysis at least 2 weeks prior to screening and plan to remain on in-center hemodialysis for the duration of the study.

   **Note 3:** Patients receiving alternate dialysis modalities such as nocturnal dialysis will not be eligible.
5. If female, is not pregnant or nursing during any period of the study;
6. If female:
   a. Is surgically sterile; or
   b. Has been amenorrhoeic for at least 1 year and is over the age of 55 years; or
   c. Has a negative serum pregnancy test within 7 days of administration of the first dose of study drug and agrees to use acceptable contraceptive measures (eg, hormonal contraceptives, barrier with spermicide, intrauterine device, vasectomized partner, or abstinence from heterosexual

intercourse) from the time of informed consent until 7 days after the last dose of study drug;

7. If male, agrees not to donate sperm after the first dose of study drug until 7 days after the last dose of study drug, and agrees to use a condom with spermicide or abstain from heterosexual intercourse during the study until 7 days after the last dose of study drug;

   **Note:** No restrictions are required for a vasectomized male provided his vasectomy was performed ≥4 months prior to screening.
8. Has a prescription dry body weight ≥40 kg;
9. Over the last three months prior to screening, has had at least one of the following:
   a. At least 2 single-pool Kt/V measurements ≥1.2 on different dialysis days;
   b. At least 2 urea reduction ratio measurements ≥65% on different dialysis days;
   c. 1 single-pool Kt/V measurement ≥1.2 and 1 urea reduction ratio measurement ≥65% on different dialysis days;
10. Prior to treatment:
    a. Has completed at least three Worst Itching Intensity Numerical Rating Scale (NRS) questionnaires from the start of the Run-in Period up to and including the assessment on Day 1;
    b. Has a mean baseline Worst Itching Intensity NRS score ≥ 5, defined as the average of all non-missing scores reported from the start of the Run-in Period up to and including the pre-dose assessment on Day 1.

**Exclusion Criteria:**

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

1. Known noncompliance with dialysis treatment that in the opinion of the Investigator would impede completion or validity of the study;
2. Scheduled to receive a kidney transplant during the study;
3. Known history of allergic reaction to opiates, such as hives;

   **Note:** side effects related to the use of opioids, such as constipation or nausea, would not exclude patients from the study.
4. Hypersensitivity to the active substance or any of the excipients in the investigational products;
5. Has a concomitant disease or a history of any medical condition that, in the opinion of the Investigator, could pose undue risk to the patient, impede completion of the study procedures, or would compromise the validity of the study measurements, including, but not limited to:
   a. Known or suspected history of alcohol, narcotic, or other drug abuse, or substance dependence within 12 months prior to screening;
   b. Significant systolic or diastolic heart failure (eg, New York Heart Association Class IV congestive heart failure [Appendix 1, Section 14.1]);
   c. Severe mental illness or cognitive impairment (eg, dementia);

d. Any other relevant acute or chronic medical or neuropsychiatric condition within 3 months prior to screening (eg, diagnosis of encephalopathy, coma, delirium);

6. New or change of treatment received for itch including antihistamines and corticosteroids (oral, IV, or topical) within 14 days prior to screening;
7. New or change of prescription for opioids, gabapentin, or pregabalin within 14 days prior to screening;
8. Received another investigational drug within 30 days or five half-lives (whichever is longer) prior to the start of dosing or is planning to participate in another interventional clinical study while enrolled in this study;
9. In the opinion of the Investigator, has pruritus attributed to a cause other than ESRD or its complications (eg, patients with concomitant pruritic dermatological disease or cholestatic liver disease);

   **Note:** Patients whose pruritus is attributed to ESRD complications, such as hyperparathyroidism, hyperphosphatemia, anemia, or the dialysis procedure or prescription may be enrolled).
10. Has localized itch restricted to the palms of the hands;
11. Has pruritus only during the dialysis session (by patient report);
12. Is receiving ongoing ultraviolet B treatment and anticipates receiving such treatment during the study;
13. Participated in a previous clinical study with CR845.

## 6.3 Removal of Patients from Therapy or Assessment

### 6.3.1 Discontinuation of Individual Patients

A patient may be withdrawn at any time and at the discretion of the Investigator or the Sponsor for safety, behavioural, compliance, or administrative reasons, including, but not limited to:

- Lost to follow-up
- Adverse event
- Lack of therapeutic efficacy
- Pregnancy
- Eligibility (inclusion/exclusion criteria)
- Patient non-compliance
- Informed consent is withdrawn

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

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

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

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

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

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

### 6.3.2 Discontinuation or Suspension of Entire Study

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

- Investigators have not been able to enroll patients within a reasonable period of time or according to inclusion/exclusion criteria;
- The target number of patients required for the study is enrolled earlier than expected;
- Unexpected safety concern.

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

Should the study be closed prematurely, all study materials must be returned to the Sponsor or destroyed at the site according to instructions provided by the Sponsor, as applicable.

## 6.4 Treatments

Detailed information on the study drug and its preparation, administration, storage, supply, disposition, and accountability can be found in the Pharmacy Manual.

### 6.4.1 Treatments Administered

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

Patients will receive CR845 three times per week for up to 12 weeks, for a total of up to 36 doses. CR845 will be administered as a 0.5 mcg/kg IV bolus into the venous line at the end of their dialysis, either during rinse back or after rinse back. If the study drug is

administered after rinse back, the line MUST be flushed with an additional 10ml normal saline to ensure study drug doesn't get stuck in the line.

Patients who require an extra hemodialysis session in a given week should receive an additional dose of CR845; if the extra session is ultrafiltration only, no additional CR845 dose should be given.

A maximum of four doses a week are allowed but patients who routinely receive 4 dialysis/ultrafiltration treatments per week will not be eligible for the study.

The patient's prescription dry body weight (ie, the target post-dialysis weight at the end of screening, as determined by the Investigator) will be used to calculate the dose of the study drug to be administered during the Treatment Period.

### 6.4.2 Identity of Investigational Product(s)

#### 6.4.2.1 Formulation of Study Drug

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

#### 6.4.2.2 Packaging, Labeling, and Storage Stability of Study Drug

Temperature will be monitored during shipment and verified and recorded by the pharmacist upon arrival at the site. The vials must be stored per pharmacy manual defined guidelines upon receipt and the temperature will be monitored accordingly. Labeling of the vials and kits will conform to the regulations required by each country.

Refer to the Pharmacy Manual for details.

#### 6.4.2.3 Individual Dose Labeling

One syringe will be prepared for each patient on each dosing day. Syringes and syringe labels will be provided.

Refer to the Pharmacy Manual for details.

### 6.4.3 Drug Accountability

All supplies will be maintained under adequate security by the approved staff at the investigational site. Study monitor will perform drug accountability on a regular basis. Details of study drug accountability are provided in the Pharmacy Manual.

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

### 6.4.4 Preparation of CR845

A single vial of CR845 will be used for patients with a prescription dry body weight ≤135.0 kg. For patients with a prescription dry body weight >135.0 kg, 2 vials of CR845 will be used to ensure that the full volume of study drug can be prepared. The syringes can be prepared up to an hour in advance of dosing.

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

### 6.4.5 Management of Missed Doses

If a patient misses a dialysis visit, dosing of study drug should resume at the next dialysis visit.

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

### 6.4.6 Treatment Compliance

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

### 6.4.7 Prior, Concomitant, and Prohibited Medications

#### 6.4.7.1 Prior and Concomitant Medications

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

Use of antipruritic medications during the study will be recorded on an ongoing basis, starting at screening. Medications known for potential antipruritic effects but used for a different indication (ex. use of gabapentin for pain management) will not be reported as antipruritic medications.

All prior and concomitant medications are to be recorded in the appropriate page of the eCRF, as applicable.

#### 6.4.7.2 Restricted and Prohibited Medications

During the Screening and Treatment Periods (as applicable), the following medications will be restricted or prohibited (Table 1).

**Table 1. Restricted and Prohibited Medications**

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

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

## 6.5 Study Assessments and Procedures

### 6.5.1 Schedule of Events for the Treatment Period

Study procedures are summarized in Table 2.

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

## Table 2. Schedule of Events

| | Screening Period (days) | | Treatment Period [f] (weeks) | | | | Early Termination Visit [d] | End of Treatment Visit [g] | Follow-Up Visit |
|---|---|---|---|---|---|---|---|---|---|
| | Screening Visit | Run-in | | | | | | | |
| | Day -28 to Day -7 | Day -7 to Day 1 | Week 1 | Week 5 | Week 9 | Week 12 | _ _ _ | Week 13 | Week 13-14 |
| **Procedures** | | | | | | | | | |
| Informed Consent | X | | | | | | | | |
| Inclusion/Exclusion Criteria [a] | X | | X | | | | | | |
| Medical History/Demographic [a,h] | X | | X | | | | | | |
| Prior Medications [a] | X | X | X | | | | | | |
| Pre-dialysis 12-lead ECG [b] | X | | | | | | X | X | |
| Pre-dialysis Vital Signs [c] | X | | X | X | X | | X | X | X |
| Serum pregnancy (females of childbearing potential) [e] | X | | | | | | X | X | |
| Patient training on PRO worksheets | X [o] | X [p] | X [p] | | | | | | |
| Questionnaires [i,j,k,l] | | X | X | | | X | X | X | |
| Physical Exam | X | | | | | | | | |
| Prescription dry body weight | X | | | | | | | | |
| Hematology, serum chemistry (pre-dialysis) | X | | X | | | | X | X | |
| IV administration of study drug | | | Dose after each dialysis up to W12 inclusive | | | | | | |
| Adverse event monitoring [m] | X | X | Record on an ongoing basis | | | | X | X | X |
| Concomitant medications [n] | | | Record on an ongoing basis | | | | X | X | X |
| Record number of missed dialysis visits and reason(s) | | Record on an ongoing basis | | | | | | | |
| Record of In-patient hospitalization and reason(s) | Record on an ongoing basis | | | | | | | | |

a Medical history, demographic and prior medications will be recorded during screening and updated on Day 1 with any changes since the Screening Visit, and inclusion/exclusion criteria will be confirmed prior to starting treatment on Day 1

b Electrocardiograms must be performed prior to the start of dialysis at screening and EOT/Early Termination Visit

c Pre-dialysis (prior to start of dialysis) vital signs, including body temperature, heart rate, and blood pressure, will be recorded when the patient is in a sitting or semi-recumbent position on the third dialysis session (Fri/Sat) of the specified week. Heart rate will be measured at each dialysis; if heart rate is clinically significant and outside the prespecified visits per the Schedule of Events, the heart rate will be recorded on the relevant CRF page

d Early Termination procedures need to be performed following the first dialysis visit after the last study dose if the patient discontinues study prior to the completion of full 12-week treatment period

e Serum pregnancy must be performed and resulted within 7 day prior to first study dose and should test for human chorionic gonadotropin (HCG)

f Each visit during the Treatment Period will coincide with the patient's normal dialysis treatments

g The End-of-Treatment Visit will be the first dialysis visit following the last dose of study drug after the patient completed the treatment period of 12 weeks

h In addition to providing a general medical history, patients will be specifically asked if they have conditions of special interest (ie, gait disturbance, fall, dizziness, somnolence, seizure, syncope, mental status changes, mood altered, feeling abnormal, tachycardia, and palpitations) and number of missed dialysis visits four weeks prior to Day 1 of run-in

i Worst Itching Intensity NRS and Sleep quality questionnaires should be completed around the start of each dialysis visit (all three sessions) during the Run-In Period & Week12. They should also be performed on the first dialysis visit (Monday/Tuesday) during Week 1 & on the first dialysis visit after the last dose of CR845. Worst Itching Intensity NRS should be completed prior to the Sleep Quality Questionnaire.

j Patients will be requested to complete their PRO questionnaires at a similar time (preferably within one hour of starting dialysis). The worksheets will be completed prior to or during dialysis, but must be completed prior to dosing

k 5-D Itch and Skindex-10 questionnaires should be completed at the first dialysis visit of Week 1 and on the first dialysis visit after the last dose of CR845. If the first visit of the week is missed, the patient may complete the worksheets at their next visit for the same week. Preferably, the 5-D Itch questionnaire is to be completed first.

l EQ-5D-5L-P questionnaire should be completed around the start of the third dialysis visit of the Run-In Period and around the start of the third dialysis visit of week 12

m Infections will be recorded as per standard procedures at the dialysis sites and reported on the adverse event eCRF page. Information pertaining to the nature of the infections will be collected

n Concomitant medications including antipruritic medication will be updated at each dialysis visit until the end of the Follow-up Visit

o Training on Worst Itching Intensity NRS, Sleep Quality, and EQ-5D-5L-P questionnaires will be conducted prior to the start of the Run-in Period

p Training on 5-D Itch and Skindex-10 questionnaires may be performed at any time during Screening Period prior to treatment on Day 1

### 6.5.2 Effectiveness Assessments

The effect of CR845 on itch and itch-related quality of life and quality of sleep will be measured by means of the following PRO questionnaires:

- Worst Itching Intensity NRS
- Sleep Quality
- Skindex-10
- 5-D Itch
- EQ-5D-5L-P

Patients will be trained on completion of the Worst Itching Intensity NRS, Sleep Quality, and EQ-5D-5L-P questionnaires prior to the first visit of the Run-in Period, and will be trained on the other itch-related PRO measures at any time prior to dosing on Day 1 of the Treatment Period. All questionnaires must be completed in strict adherence to the Training Manual for Patient Reported Assessments. Patients will be provided with these questionnaires to complete at the clinic on specific dialysis days per the schedule of events (Table 2).

#### 6.5.2.1 Worst Itching Intensity Numerical Rating Questionnaire

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."

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

#### 6.5.2.2 Sleep Quality Questionnaire

The impact of itch on patients' quality of sleep will be measured using an NRS scale (Appendix 3, Section 14.3) on a worksheet on which patients will be asked to indicate how their itch interferes with their sleep 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 "did not interfere" and "10" is labeled "completely interfered"

#### 6.5.2.3 Skindex-10 Questionnaire

Developed specifically for pruritus associated with chronic kidney disease, the Skindex-10 (Appendix 4, Section 14.4) is an instrument for measurement of quality-of-life that correlates with itch intensity [Mathur 2010]. Patients are asked to mark 1 of 7 boxes

numbered from 0 (labeled with the anchor phrase "never bothered") to 6 (labeled as "always bothered") for each of the 10 questions describing how often they have been bothered by their itch and its impact over the past week. The total score is the sum of the numeric value of each answered question. The total score is subdivided into 3 domain scores, which are sums of the scores of the following questions: disease domain (questions 1 to 3), mood/emotional distress domain (questions 4 to 6), and social functioning domain (questions 7 to 10).

#### 6.5.2.4 5-D Itch Questionnaire

The 5-D Itch Scale was developed as a brief, multidimensional questionnaire designed to be useful as an outcome measure in clinical studies. The 5 dimensions of itch assessed are degree, duration, direction, disability, and distribution (Appendix 5, Section 14.5). Patients are asked to mark boxes that best describe the impact of their itch over the past 2 weeks. The scale has been validated in patients with chronic pruritus, including hemodialysis patients and has been shown to be sensitive to changes in pruritus over time [Elman 2010].

#### 6.5.2.5 EQ-5D-5L-P Questionnaire

The 5-level EQ-5D questionnaire (EQ-5D-5L) was introduced by the EuroQol Group in 2009. The EQ-5D-5L (Appendix 6, Section 14.6) essentially consists of 2 questionnaires: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS).

The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The patient is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the five dimensions.

The EQ VAS records the patient self-rated health on a vertical visual analogue scale, with values ranging from "The best health you can imagine" and "The worst health you can imagine."

The EQ-PSO (Pruritis bolt-on) will be added to the EQ-5D-5L includes two additional dimensions "skin irritation" and "self-confidence" to better capture the itch associated burdens [Swinburn 2013].

### 6.5.3 Safety Assessments

The safety assessments for each patient are the following:

- Severity, seriousness, and relationship of adverse events to study drug
- Vital signs

- 12-lead ECGs
- Clinical laboratory tests

#### 6.5.3.1 Adverse Events

**Definition of Adverse Events**

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

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

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

A pre-existing condition is a condition that is present prior to signing the ICF for the study. Pre-existing conditions, such as illnesses, symptoms, reactions, progression of disease states, and other comorbidities, as well as laboratory/diagnostic test abnormalities, will be documented in the patient's record as medical history. In addition to general history, patients will be specifically asked if they have a history of certain conditions including but not limited to gait disturbances, falls, dizziness, somnolence, seizures, syncope, mental status changes, mood alterations, palpitations and tachycardia.

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

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

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

### Adverse Event Severity Assessment

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

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

### Definition of Serious Adverse Events

An SAE is any untoward medical occurrence that:

- Results in death;
- Is life-threatening;

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

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

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

### Severe versus Serious Adverse Event

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

threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

**Adverse Event Causality or Relatedness to the Study Drug**

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

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

**Adverse Event Documentation and Follow-up**

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

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

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

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

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

**Serious Adverse Event Notification, Documentation, and Reporting**

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

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

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

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

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

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

As applicable, the Sponsor will also notify other participating Investigator(s) of SUSARs 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.

#### 6.5.3.2 Physical Examination

Physical examinations at Screening will include an examination of the heart, lungs, abdomen, extremities, and neurological and vascular systems. Any findings should be reported in the medical history.

#### 6.5.3.3 Vital Signs

Vital signs (sitting or semi-recumbent body temperature, heart rate, and blood pressure) will be measured prior to start of dialysis as per schedule presented in Table 2.

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

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

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

#### 6.5.3.4 Electrocardiogram

The 12-lead ECGs will be obtained prior to the start of dialysis and will be read locally by the Investigator or qualified designee as per schedule presented in Table 2. Electrocardiograms read by a qualified designee must be endorsed by the Investigator. Clinically significant abnormalities or worsening findings observed after the first dose of study drug will be reported as treatment-emergent adverse events (TEAEs).

#### 6.5.3.5 Clinical Laboratory Tests

Blood samples for clinical laboratory tests including hematology, serum chemistry, and serum pregnancy will be taken prior to dialysis as per schedule presented in Table 2 and will be analyzed by a central laboratory. The laboratory tests include the following:

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

| | |
|---|---|
| Serum Pregnancy (females of childbearing potential only) | Human chorionic gonadotropin (HCG) |

No more than 10 mL will be taken for each blood test. Processing and shipment of central laboratory samples will be described in the Laboratory Manual.

#### 6.5.3.6 Contraception and Pregnancy

All females of childbearing potential will have blood samples taken at Screening for serum pregnancy testing and at the end of the study as per Table 2. Females are considered to be of childbearing potential unless they are:

- Surgically sterile (ie, tubal ligation, bilateral oophorectomy, and/or hysterectomy); or
- Over 55 years of age and have not had a menstrual period in at least 1 year

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

Medically acceptable methods of birth control include abstinence, vasectomized partner, hormonal contraceptives for at least 1 cycle of treatment before study enrollment, an intrauterine device, and barrier with spermicide (eg, male or female condom, or diaphragm).

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

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

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

be collected from the patient while respecting the confidentiality of the partner. A pregnancy report will be completed.

## 6.6 Additional Assessments

The following additional assessments will be collected during the Treatment Period:

- Missed dialysis visits
- Hospitalizations
- Infections

### 6.6.1.1 Missed Dialysis Visits

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

### 6.6.1.2 Hospitalization

In-patient hospitalizations (including duration) will be collected on the SAE and eCRF forms.

### 6.6.1.3 Infections

Infections will be recorded as per standard procedures at the dialysis sites and reported on the adverse event eCRF page. Additional information pertaining to the nature of the infections will be collected as applicable.

# 7.0 Discussion and Justification of Study Design

This is an open-label study designed to evaluate the safety and effectiveness of CR845 0.5 mcg/kg IV administered after each dialysis session (generally 3 times per week for up to 12 weeks) in hemodialysis patients. This design is commonly used in clinical development to obtain additional safety information regarding a novel investigational drug.

## 7.1 Selection of Doses in the Study

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

## 7.2 Appropriateness of Measurements

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

# 8.0 Statistical Methods

## 8.1 General Considerations

This section describes the statistical analysis of safety, effectiveness, and additional endpoints collected during the study.

The statistical analysis plan (SAP) will provide a detailed description for the handling of missing data, patient eligibility criteria for the analysis, and statistical methodology. If differences occur between analyses of 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

Up to 400 male and female hemodialysis patients who have not been previously exposed to CR845 will be enrolled in this study. No sample size calculation was performed to select this sample size.

## 8.3 Interim Analysis

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

## 8.4 Analysis Populations

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

The Safety population is defined as the group of patients who received at least 1 dose of CR845 in the study.

The Full Analysis population is defined as the group of patients who received at least 1 dose of CR845 and have least one non-missing effective endpoint assessment after baseline.

All summaries and analysis of safety will be conducted using the Safety population.

Effectiveness endpoints analysis will be conducted using the Full Analysis population. There will be two sets of analysis for the effectiveness endpoints: main analysis and

ancillary analysis. Patients who complete the study and do not have missing data will be included in the main analysis. Patients who either discontinue early or have missing data will be include in the ancillary analysis.

## 8.5 Statistical Summary and Analysis

### 8.5.1 Patient Disposition

The number of patients who enrolled in the study, who received at least one dose of study drug, completed, or discontinued from the study drug prematurely, along with the reason for discontinuation, will be presented. The percentage of patients who completed or discontinued will be based on the safety population.

### 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. All protocol deviations will be listed.

### 8.5.3 Demographic and Baseline Characteristics

Demographic and baseline patient characteristics to be summarized, will include age at screening, age category (<45, 45 to >65, 65 to <75, ≥75), gender, ethnicity, race, and prescription dry body weight (kg).

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

### 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) and Preferred Term. The data will also be listed, including the verbatim investigator description of the relevant medical condition, the coded terms (SOC, Preferred Term), start date, end date, and whether or not the condition is ongoing.

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

### 8.5.5 Prior and Concomitant Medications

All medications will be coded using the World Health Organization Drug Dictionary. All prior and concomitant medications will be listed and summarized separately by

Anatomical Therapeutic Chemical class 3 (ATC 3) and Preferred Term. Additionally, a coding listing of unique medications and their corresponding coding will be presented.

### 8.5.6 Antipruritic Medication

Antipruritic medications are identified as medications where 'Yes' is checked on the Previous or Concomitant Medications CRF page to the question 'Medication was given to treat pruritus'.

Prior and concomitant antipruritic medications will be summarized separately. Summaries will be presented by ingredient rather than by ATC codes.

## 8.6 Effectiveness Endpoints and Analysis

### 8.6.1 Endpoints

**24-hour Worst Itching Intensity NRS score**

- Change from baseline in the weekly mean of the 24-hour Worst Itching Intensity NRS score to Week 12.
- Proportion of patients achieving >0, ≥1, ≥2, ≥3, and ≥4-point improvement from baseline with respect to the weekly mean of the daily 24-hour Worst Itching Intensity NRS at Week 12.

**Sleep Quality Questionnaire**

- Change from baseline in the weekly mean of the 24-hour Sleep Quality score to Week 12.

**5-D Itch and Skindex-10 Questionnaires**

- Change from baseline in itch-related quality of life to Week 12 as assessed by the 5-D Itch total score and each 5-D Itch individual questions.
- Change from baseline in itch-related quality of life to Week 12 as assessed by the total Skindex-10 total score and each Skindex-10 subdomain score (disease, mood/emotional distress, social functioning).

**EQ-5D-5L Questionnaire**

- Proportion of patients with reported problems by level (1 to 5) and EQ-5D-5L dimension will be summarized at baseline and Week 12.
- Proportion of patients with no problems (i.e. with a level 1 response) by EQ-5D-5L dimension will be summarized at baseline and Week 12.
- Overall Self-Rated Health Status EQ VAS will be summarized (mean, SD, median, Q25-Q75) at baseline and at Week 12 along with the change from baseline.

- Patients **health state** will be expressed using the 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is evaluated using 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. Response to these 5 dimensions will be converted into 1 of 3125 unique EQ-5D-5L health state descriptions, which ranges between no problems on all 5 dimensions (11111) to extreme problems on all 5 dimensions (55555). The patients' health state will be displayed in a listing.

**EQ-PSO Questionnaire**

- Proportion of patients with reported problems by level (1 to 5) and EQ-PSO dimension will be summarized at baseline and Week 12.
- Proportion of patients with no problems (i.e. with a level 1 response) by EQ-PSO dimension will be summarized at baseline and Week 12.

### 8.6.2 Analysis

The weekly mean of the 24-hour Worst Itching Intensity NRS score at Week 12 will be defined as the sum of the Worst Itching Intensity NRS scores collected on each dialysis visit of Week 12 and on the first dialysis visit of Week 13, divided by the number of days with non-missing scores for that week. The baseline score will be defined as the average of the daily 24-hour Worst Itching Intensity NRS scores collected over the Run-in Period, including assessments collected on Day 1 prior to the first dose of the Treatment Period. For the analysis of NRS, if the 24-hour daily Worst Itching Intensity score is missing for >2 dialysis during the collection period on Weeks 12 and 13 then the corresponding weekly mean worst itching score will be set to missing.

Summary statistics (n, mean, SD, min, max) for the weekly mean of the 24-hour Worst Itching Intensity NRS score at baseline and at Week 12 of the Treatment Period along with the change from baseline will be produced. In addition, the change from baseline in the weekly mean of the 24-hour Worst Itching Intensity NRS score to Week 12 Treatment Period will be analyzed using analysis of covariance (ANCOVA). The model will contain baseline score as covariate. LS means, standard errors, and 95% confidence intervals (CI) derived from the model will be presented. The same procedure will be used to analyse Sleep Quality.

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 >0, ≥1, ≥2, ≥3, and ≥4 points at Week 12 will be analysed using a logistic regression model containing baseline NRS score. A figure presenting the proportion of patients who have an improvement from baseline in NRS scores at Week 12 that is >0, ≥1, ≥2, ≥3, and ≥4 will be prepared.

The 5-D Itch and the Skindex-10 questionnaires total score and domains/individual questions will be summarized using summary statistics and analysed using a ANCOVA

as described for the 24-hour Worst Itching Intensity NRS score. For the analysis of 5-D Itch and the Skindex-10 scores, missing scores will not be imputed.

It is important to note that, in HD patients, the study drug administered during the last dialysis of a particular week does not begin to be cleared until the first dialysis of the next week. Therefore, measurements that would reflect treatment effect at the end of a specific week (eg. Week 12) will actually be collected during the first day of the next week (eg, Week 13).

Counts and percentages of subjects for each response will be reported as well as a count of subjects with missing values.

## 8.7 Safety Analysis

Analysis of all safety data collected during the Treatment Period will be performed on the Safety Population. The SAP will provide further detail for the analyses to be applied to each safety parameter. No statistical hypothesis testing will be carried out and no inferential statistical analysis of the safety parameters will be performed.

The baseline value for all analyses of Treatment Period 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 up to 36 doses of study drug administered immediately following each dialysis session. 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 dialysis session immediately following the last injection of study drug.

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

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

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

If a patient receives additional dialysis during a given week for any reason, an additional dose of CR845 will be administered following dialysis. A maximum of 4 doses per week is allowed if an infrequent occurrence. No additional doses will be given for patients

receiving an additional unscheduled ultrafiltration treatment. The number of patients getting such an extra treatment will be summarized.

### 8.7.2 Adverse Events

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

All reported adverse events (whether or not treatment-emergent) will be included in a by-patient adverse event listing. Only TEAEs will be included in summary tables.

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.

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 Follow-up Visit or Early Termination Visit (or 7 days after the last dose if no Early Termination Visit was conducted), whichever is later.

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

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

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

An overall summary table will be provided including 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 for each specific Preferred Term.

Separate tables summarizing the incidence of AESIs will be presented for Run-In and Treatment Period. Selected preferred terms will be determined prior to database lock and combined into the following categories:

- Gait disturbance
- Fall

- Dizziness
- Somnolence
- Seizure
- Syncope
- Mental status changes
- Mood altered
- Feeling abnormal
- Tachycardia
- Palpitations

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

### 8.7.3 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 ECGs

Summary tables will include descriptive statistics for baseline and each postbaseline assessment. Descriptive statistics will be calculated on both the actual score and the

change from baseline score. Baseline is defined as the last measurement taken on or prior to the first day of dosing. Note that the Day 1 assessment can be included in the evaluation of baseline if that the assessment is performed prior to dosing.

If two or more evaluations occur in the same visit window, the evaluation closest to the target visit day will be selected for inclusion in the analysis. If multiple evaluations are equally close to the target visit day, then the latest evaluation will be selected for inclusion in the analysis.

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

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

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

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

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

## 8.8 Additional Analyses

### 8.8.1 Missed Dialysis Visits, Hospitalizations and Incidence of Infection

The number and percentage of patients who missed one or more dialysis visits during the Treatment Period, and the total number of missed dialyses visits will be tabulated.

Incidence of infections based on adverse events and/or use of antibiotics for treatment of infection overall or related to pruritus will be presented.

The number and percentage of patients hospitalized during the Treatment Period, and the total number of hospitalization days will be tabulated.

# 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 but not limited to remote and onsite review of the eCRFs via an electronic data capture system for completeness and clarity, source document verification, evaluation of protocol adherence, appropriate documentation of informed consent procedures, safety reporting, study drug storage, and dispensation. The study will be monitored by the Sponsor or its designee (contract research organization). Monitoring will be performed by a representative of the Sponsor or its designee (site monitor) who will review patient enrollment, eCRFs, source documents, drug accountability records, and reporting and recording of adverse events. The site monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent site visits and communications (letter, telephone, and facsimile).

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

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

## 9.2 Audits and Inspections

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

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

## 9.3 Data Collection, Validation, and Analysis

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

# 10.0 Ethics and Regulatory Compliance

## 10.1 Independent Ethics Committee or Institutional Review Board

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

The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of the patients. The study will only be conducted at a site where IRB/IEC approval has been obtained.

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

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

## 10.2 Ethical Conduct of the Study

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

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

## 10.3 Informed Consent Process

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

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

## 10.4 Patient Confidentiality

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

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

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

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

# 11.0 Data Handling and Quality Assurance

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

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

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

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

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

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

# 12.0 Administrative Procedures

## 12.1 Protocol Adherence

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

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

## 12.2 Publication of Study Findings

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

# 13.0 References

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# 14.0 Appendix

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

**New York Heart Association (NYHA) Classification of Heart Failure**

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

[Criteria Committee of the New York Heart Association 1994]

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

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

**INSTRUCTIONS**

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

**Worst Itching Over the Past 24 Hours**

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

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

**NO ITCHING** — **WORST ITCHING IMAGINABLE**

**Date Completed:**

| D | D | M | M | M | Y | Y | Y | Y |
|---|---|---|---|---|---|---|---|---|
| | | | | | 2 | 0 | | |

**Time:**

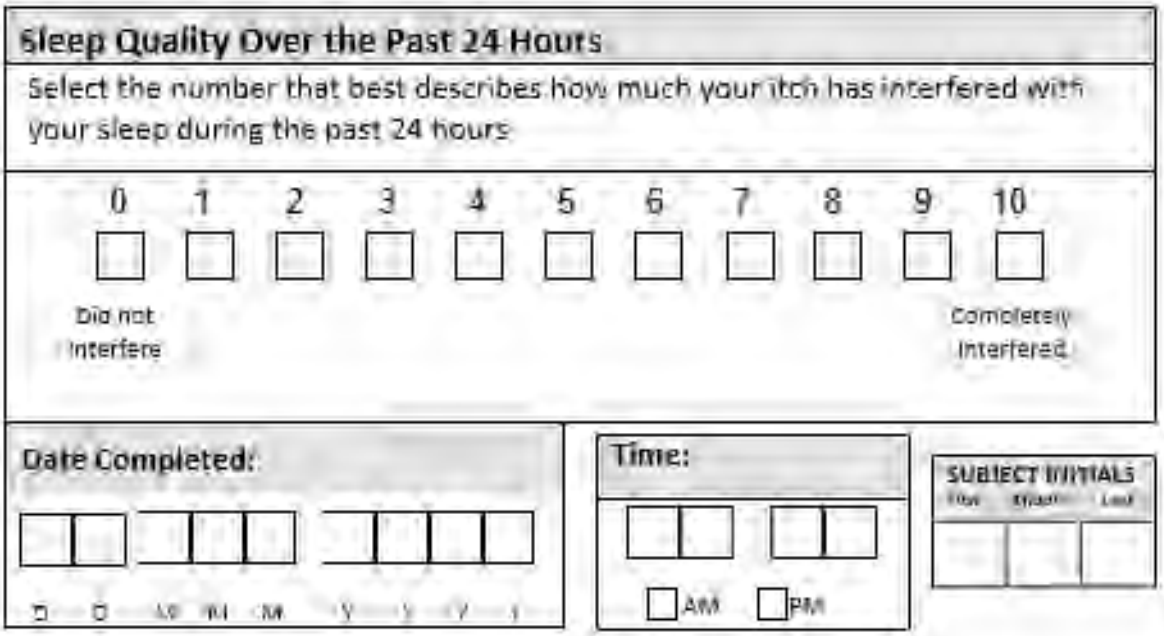
☐☐ : ☐☐ ☐ AM ☐ PM

**SUBJECT INITIALS**

| *First* | *Middle* | *Last* |
|---|---|---|
| | | |

## 14.3 Appendix 3: Sleep Quality Questionnaire

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.



## 14.4 Appendix 4: Skindex-10 Questionnaire

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* |
|---|---|---|
| | | |

## 14.5 Appendix 5: 5-D Itch Questionnaire

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 | | | | |
| | | Never affects sleep | Occasionally delays falling asleep | Frequently delays falling asleep | Delays falling asleep and occasionally wakes me up at night | Delays falling asleep and frequently wakes me up at night |
| | **Sleep** | ☐ | ☐ | ☐ | ☐ | ☐ |
| | | 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*
☐☐☐

## 14.6 Appendix 6: EQ-5D-5L-P Questionnaire

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.

EQ-5D-5L:

Under each heading, please tick the ONE box that best describes your health **TODAY**

**MOBILITY**

- I have no problems in walking about ☐
- I have slight problems in walking about ☐
- I have moderate problems in walking about ☐
- I have severe problems in walking about ☐
- I am unable to walk about ☐

**SELF-CARE**

- I have no problems washing or dressing myself ☐
- I have slight problems washing or dressing myself ☐
- I have moderate problems washing or dressing myself ☐
- I have severe problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

**USUAL ACTIVITIES** (e.g. work, study, housework, family or leisure activities)

- I have no problems doing my usual activities ☐
- I have slight problems doing my usual activities ☐
- I have moderate problems doing my usual activities ☐
- I have severe problems doing my usual activities ☐
- I am unable to do my usual activities ☐

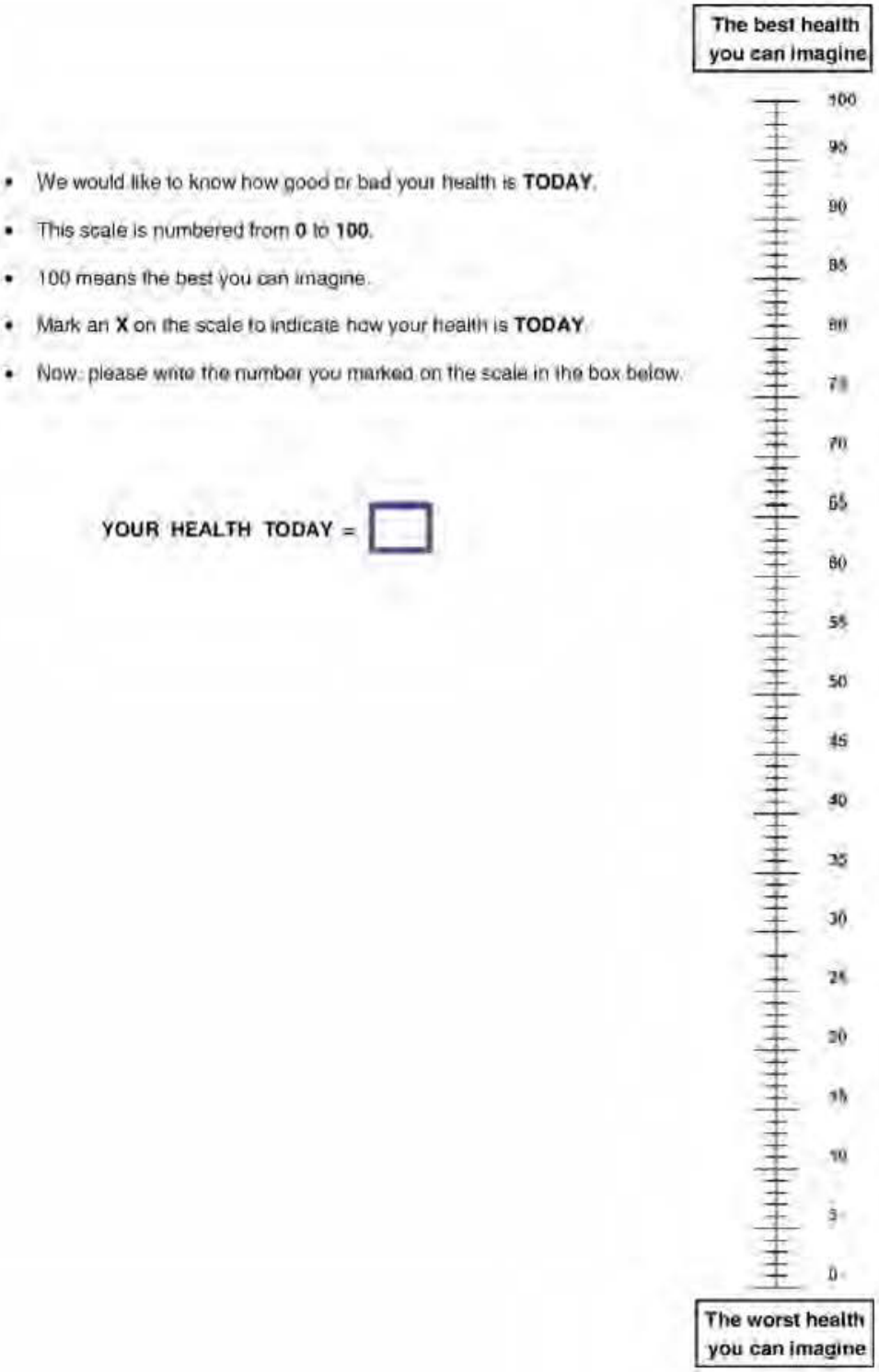
**PAIN/DISCOMFORT**

- I have no pain or discomfort ☐
- I have slight pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have severe pain or discomfort ☐
- I have extreme pain or discomfort ☐

**ANXIETY/DEPRESSION**

- I am not anxious or depressed ☐
- I am slightly anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am severely anxious or depressed ☐
- I am extremely anxious or depressed ☐

EQ VAS:


The best health you can imagine
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
The worst health you can imagine
We would like to know how good or bad your health is TODAY.
This scale is numbered from 0 to 100.
100 means the best you can imagine.
Mark an X on the scale to indicate how your health is TODAY.
Now, please write the number you marked on the scale in the box below.
YOUR HEALTH TODAY =

EQ-PSO Bolt on:

**Skin irritation (e.g. itching)**

I have no itching ☐
I have slight itching ☐
I have moderate itching ☐
I have severe itching ☐
I have extreme itching ☐

**Self-confidence**

I have no problems with self confidence ☐
I have slight problems with self confidence ☐
I have moderate problems with self confidence ☐
I have severe problems with self confidence ☐
I have extreme problems with self confidence ☐