STATISTICAL ANALYSIS PLAN
09 March 2020 Final

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

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DOCUMENT VERSION CONTROL

Version Number	Date	Comments/Changes
1.0	13 December 2019	
1.1	09 March 2020	• SMQ analyses removed • Correction to potassium normal range and hemoglobin units • Added AE analyses by region • Added WI-NRS and Sleep Questionnaire analyses by region • Removed ANCOVA and logistic regression • Minor edits and clarifications

APPROVALS

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AESI	adverse event of special interest
CI	confidence interval
CKD	chronic kidney disease
CMQ	Custom MedDRA Query
CRF	case report form
ECG	electrocardiogram
ESRD	end-stage renal disease
EQ-5D-5L	5-level EQ-5D version
EQ-5D-5L-P	EQ-5D-5L with EQ-PSO bolt-on
EQ-PSO	EQ Pruritus Bolt-on
EQ VAS	EQ visual analogue scale
H	above laboratory reference range
IV	intravenous or intravenously
L	below laboratory reference range
MedDRA	Medical Dictionary for Regulatory Activities
N	within laboratory reference range
QALY	quality-adjusted life year
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WI-NRS	Worst Itching Intensity numerical rating scale

LIST OF IN-TEXT TABLES

1. PURPOSE OF THE ANALYSES

CR845-CLIN3105 is an open-label, multicenter study to evaluate the safety and effectiveness of IV CR845 in hemodialysis subjects with moderate-to-severe pruritus. Treatment with IV CR845 at a dose of 0.5 mcg/kg is administered after each dialysis session over a Treatment Period of up to 12 weeks. This study is sponsored by Cara Therapeutics, Inc. ("Sponsor").

This statistical analysis plan (SAP) provides a detailed description of the strategy and statistical methodology to be used for analysis of data in the CR845-CLIN3105 protocol.

The purpose of the SAP is to ensure the credibility of the study findings by pre-specifying the statistical approaches to the analysis of study data prior to database lock. This analysis plan is meant to supplement the study protocol. If differences occur between analyses described in the SAP and the current protocol, those found in this SAP will assume primacy. Any deviations from this plan will be described in the Clinical Study Report.

2. PROTOCOL SUMMARY

2.1 Study Objectives

The primary objective of the study is to evaluate the safety of IV CR845 at a dose of 0.5 mcg/kg in hemodialysis subjects with moderate-to-severe pruritus. The secondary objectives are to evaluate the effectiveness of IV CR845 at a dose of 0.5 mcg/kg in reducing the intensity of itch in hemodialysis subjects with moderate-to-severe pruritus and in improving itch-related quality-of-life and quality of sleep measures in hemodialysis subjects with moderate-to-severe pruritus.

2.2 Overall Study Design and Plan

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, subjects will be required to complete a Follow-up Visit.

2.2.1 Screening Period

The Screening Visit will occur within 21 days 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.

Subjects will start the Run-in Period during the week prior to the Treatment Period to complete eligibility verification. The Run-in Period will start on the first dialysis session of that week (ie, Monday for subjects on a Monday-Wednesday-Friday dialysis schedule or Tuesday for subjects on a Tuesday-Thursday-Saturday dialysis schedule). The primary purpose of the Run-in Period is to confirm that each subject has moderate-to-severe pruritus (ie, weekly average Worst Itching Intensity Numerical Rating Scale (WI-NRS) $\geq$5) and to establish a baseline itch intensity.

If subjects 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.

2.2.2 Treatment Period

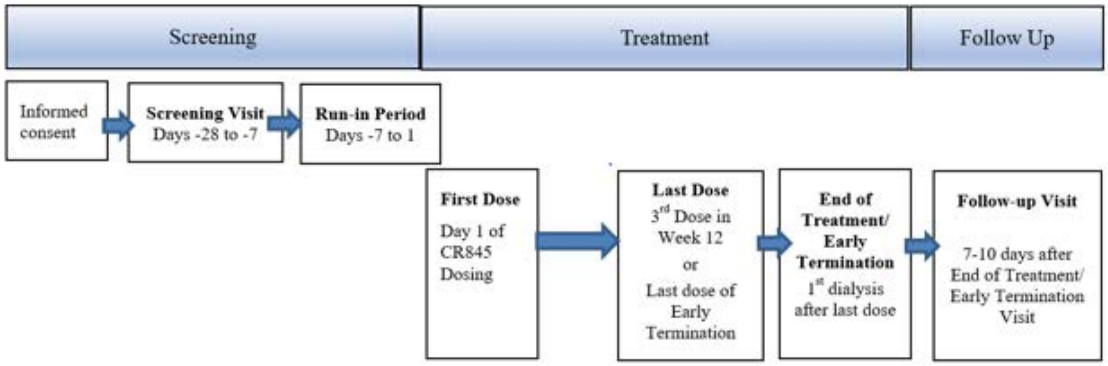
Day 1 of the Treatment Period will be defined as the day of administration of the first dose of study drug and will occur on the first dialysis day of the first treatment week. Each subject will receive CR845 at a dose of 0.5 mcg/kg after each dialysis session, 3 times per week for up to 12 weeks and up to 36 doses of study drug. All scheduled study visits during the Treatment Period will be conducted on dialysis days. Subjects 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.

End of Treatment is defined as the first day of dialysis following the last dose of drug and will be considered the last day of the Treatment Period. The End of Treatment procedures will be conducted at the dialysis visit following the last dose.

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

The study schematic is shown below:



2.3 Study Population

The study population includes males and females between 18 and 85 years of age, inclusive, with end-stage renal disease (ESRD) who have been on hemodialysis 3 times per week for at least 3 months prior to start of screening, have moderate-to-severe pruritus (mean baseline WI-NRS score ≥5 with at least 3 worksheets completed from the start of the Run-in Period up to and including the pre-dose assessment on Day 1), and meet additional eligibility criteria. A full list of the inclusion and exclusion criteria can be found in the CR845-CLIN3105 protocol (v2.0 12FEB2019).

Subjects providing informed consent will be screened for inclusion in the study; all eligibility criteria must be met before a subject receives the first dose of study drug. Rescreening will be considered on an individual-subject basis and must first be approved by the Sponsor or Medical Monitor, provided that rescreening will not be permitted if a subject misses the entry criteria for itch intensity. A subject can only be rescreened once, and rescreening can only occur after at least 2 weeks from original Screening Visit.

2.4 Treatment Regimens

Subjects 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. Subjects who require an extra hemodialysis session in a given week should receive an additional dose of CR845, unless

the extra session is ultrafiltration only. A maximum of 4 doses a week are allowed, but subjects who routinely receive 4 dialysis/ultrafiltration treatments per week will not be eligible for the study.

2.5 Treatment Group Assignments or Randomization

As this is an open-label, single-arm treatment study, all subjects will be assigned to a dose of 0.5 mcg/kg, and no randomization will occur.

2.6 Sample Size Determination

Approximately 200 male and female hemodialysis subjects with moderate-to-severe pruritus will be enrolled in this study at approximately 50 U.S. and non-U.S. clinical sites. No sample size calculation was performed to select this sample size.

3. GENERAL ANALYSIS AND REPORTING CONVENTIONS

This section discusses general policies to be employed in the analysis and reporting of the data from the study. Departures from these general policies may be given in the specific detailed sections of this SAP. When this situation occurs, the rules set forth in the specific section take precedence over the general policies.

Treatment groups: All subjects will receive open-label CR845 0.5 mcg/kg; thus displays will present tabulations of all subjects in a single column.

For categorical variables, summary statistics will consist of the number and percentage of subjects in each category. All percentages will be rounded to 1 decimal point. The number and percentage of subjects will always be presented in the form XX (XX.X%) with the percentage in parentheses. To ensure completeness, all summaries for categorical and discrete variables will include all categories, even if none of the subjects had a response in a particular category. Unless otherwise noted, for all percentages, the number of subjects in the specified analysis population will be the denominator.

For continuous variables, summary statistics will consist of the number of subjects with data, mean, median, standard deviation, minimum value, and maximum value. The summary statistic n will be the number of subjects with non-missing values. All means and medians will be reported to 1 more significant digits than the values being analyzed. Standard errors will be reported to 2 more significant digits than the values being analyzed. The minimum and maximum will be reported to the same number of significant digits as the values being analyzed.

No formal hypothesis tests are planned; however, should they be performed as part of exploratory and ad hoc analyses, the associated *P* value will be reported. All *P* values will be rounded to 3 decimal places; *P* values that round to 0.000 will be presented as "<.001". No leading zero will be shown for *P* values. *P* values will be considered descriptive in nature; there will be no adjustments for multiple comparisons.

In general, and unless otherwise specified, the baseline value will be considered the last non-missing measurement observed prior to the first dose of study drug

Data from all sites will be pooled for the purpose of analysis.

In general, listings will be sorted in the order that columns are displayed, starting with the first column on the left (treatment). Subject listings of data will be presented for all enrolled subjects unless specified otherwise.

SAS statistical software, version 9.4 or higher, will be used for all analyses.

3.1 Assessment Time Windows

Assessments collected by study week that are collected at the Early Termination Visit or unscheduled visits will be assigned to a planned visit window, if the Early Termination Visit or unscheduled visit day falls between ±3 days of the planned visit. Exceptions to

this assignment include the Week 13 visit, which will use a window of +1/-3; Day 1, which is anchored by the first dose; run-in WI-NRS and Sleep Quality scores, which will be assigned to the nearest planned visit; and where otherwise specified in this SAP.

Should more than 1 measurement fall within a visit window, priority will be given first to the measurement with a non-missing value in the following order: first the scheduled assessment, second to an Early Termination Visit, and then the unscheduled assessment closest to the planned day. In the case that 2 unscheduled visits are equidistant, the latest will be used.

This rule will be applied to both effectiveness and safety endpoints.

4. ANALYSIS POPULATIONS

The Enrolled Population is defined as the group of subjects who signed informed consent.

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

All summaries and analyses of safety, effectiveness and additional endpoints will be conducted using the Safety Population.

5. STUDY SUBJECTS

5.1 Disposition of Subjects

The number of subjects enrolled, screen failed, treated, completed, or discontinued from the study treatment, along with the reasons for treatment discontinuation and screen failure, will be presented. Subjects completing follow-up will also be presented. The number of subjects included the Safety Population will also be tabulated.

The following definitions apply to the afore-mentioned groups:

- Enrolled subjects are all subjects who signed informed consent (see Section 4).
- Subjects who failed screening are all subjects who failed screening due to inclusion/exclusion criteria and are marked as such on the disposition CRF. Subjects who fail screening and are rescreened and enrolled will be counted both here and with the applicable outcome of their successful enrollment. Those who screen fail twice will be counted only once here; their reported reasons for failure will be from their final failure.
- Treated subjects are all subjects who received at least 1 dose of study drug.
- Treatment completers are treated subjects with "Yes" noted for the question "Did the Subject complete the Treatment Period?" on the *Study Completion Status* case report form (CRF) page.
- Subjects who discontinued the treatment are subjects with "No" noted for the question "Did the Subject complete the Treatment Period?" on the *Study Completion Status* CRF page. Reasons for treatment discontinuation are also collected on this CRF.
- Follow-up completers are treated subjects with "Yes" noted for the question "Did the Subject complete the Follow-up Visit?" on the *Study Completion Status* CRF page.
- Safety Population includes any treated subject (see Section 4).

For all categories of subjects (except for enrolled subjects and screen failure subjects), percentages will be calculated using the number of subjects in the Safety Population as the denominator.

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. Deviations will be classified as minor or major prior to the database lock. Protocol deviations/violations will be summarized. All protocol deviations will be listed.

6. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic and baseline characteristics are collected during the Screening Visit.

Descriptive statistics will be provided for all demographic and baseline characteristics based on the Safety Population. For categorical variables, the number and percentage of subjects in each category will be presented. For continuous variables, summaries will include the number of subjects with data, mean, median, standard deviation, minimum, and maximum.

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

6.1 Demographic Characteristics

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

- Age at screening (years) as recorded on the CRF
- Age category at screening (<45, 45-<65, 65-<75, ≥75 years)
- Gender
- Ethnicity
- Race
- Target dry body weight (kg)
- Country
- Region: USA, Western (Canada, UK, Germany, Australia, New Zealand), Eastern EU (Poland, Hungary, Romania, Czech Republic), Asia (Taiwan, South Korea)

6.2 Baseline Characteristics

Baseline characteristics of the disease will also be summarized and include the following:

- Prior anti-itch medication use
- Duration of pruritus (years)
- Years since diagnosis of ESRD
- Years since diagnosis of chronic kidney disease (CKD)
- Years on chronic hemodialysis
- Etiology of CKD
- Baseline WI-NRS Score
- Dialysis type
- Dialysis type by region

Duration of pruritus (years) will be calculated as:

(Date of the Screening Visit – the start date of the pruritus + 1)/365.25

Similarly, years since diagnosis of ESRD will be calculated as:

(Date of the Screening Visit – first date of ESRD diagnosis + 1)/365.25

Years since diagnosis of CKD will be calculated as:

(Date of the Screening Visit – first date of CKD diagnosis + 1)/365.25

Years on chronic hemodialysis will be calculated as:

(Date of the Screening Visit – date of first chronic hemodialysis + 1)/365.25

For each of the above, if partial dates are recorded, the first day of the month will be imputed for missing day, and January for missing month.

The baseline WI-NRS score is defined as the average of the WI-NRS scores collected over the Run-in Period starting at Day -7, including assessments collected on Day 1 prior to the first dose of the Treatment Period. Subjects should provide at least three NRS values in the period from Day -7 to Day 1; however, if fewer are present in the data, any available values will be used for establishing the baseline.

6.3 Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 22.0 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.

6.4 Prior and Concomitant Medications

All medications, including any anti-itch medications, are recorded at screening, and the record is updated at each dialysis visit until the end of the Follow-up Visit. These will be coded using the March 2019 *World Health Organization Drug Dictionary*. All prior and concomitant medications will be listed. Additionally, a listing for unique medications and their corresponding coding will be presented.

6.4.1 Prior Medication

Prior medications (including vitamins and herbal supplements) are defined as medications collected on the *Previous or Concomitant Medications* CRF page that the subject has taken any time during the last 3 months prior to the first dose of study drug on

Day 1. If the medication started prior to treatment start date, but was ongoing or ended after treatment start date, the medication will be counted as both prior and concomitant. Prior medications will be summarized in a table using the Safety Population. Medications will be reported by drug class (Anatomical Therapeutic Chemical Level 3) and ingredient; a subject will be counted only once for each medication. In the case of partial dates, if the available information is consistent with a date prior to the first dose, then the medication will be included on the summary of prior medications.

6.4.2 Concomitant Medication

Concomitant medications are defined as medications collected on the *Previous or Concomitant Medications* CRF page that are taken (regardless of when they started) from after the start of the first dose of study drug on Day 1 through the end of the study (ie, Follow-Up Visit). Concomitant medications will be summarized for the Safety Population. Medications will be reported by drug class (Anatomical Therapeutic Chemical Level 3) and ingredient; a subject will be counted only once for each medication. In the case of partial dates, if the available information is consistent with dates overlapping with the period study drug was taken, then the medication will be included on the summary of concomitant medications.

6.4.3 Anti-itch Medication

Anti-itch 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?" or if "Pruritus" was listed on the CRF page under "Other Indication".

The prior and concomitant medication summaries described in Sections 6.4.1 and 6.4.2 will be repeated for the anti-itch medications but will be reported by ingredient only and not by drug class.

7. MEASUREMENTS OF TREATMENT COMPLIANCE

For this study, the duration of treatment for each individual subject is expected to be 12 weeks, for a total of approximately 36 doses of study drug administered immediately following each dialysis session.

The following variables will be summarized:

- Duration of treatment (days)
- Duration of study, from first dose to end of participation date (days)
- Average dose per administration (mcg/kg)
- Total number of doses actually received (1-3, 4-6, 7-9, etc.)
- Number of missed doses
- Total number of dialysis visits logged (1-3, 4-6, 7-9, etc.)
- Number of missed dialysis visits
- Total treatment exposure in subject-years
- % Compliance (Doses)
- % Compliance (Dialyses)
- Number of subjects with extra doses
- Number of subjects with extra dialysis visits

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

Duration of study (days) = [(End of participation date, including follow-up) – (Date of first dose) + 1]. The end of participation date is derived as the latest of the last visit date, the last drug exposure, the latest disposition date, or the death date. If the subject has a death date, any later dates in the database are ignored.

Subject-years = Duration of treatment (days) of all subjects divided by 365.25.

% Compliance (Doses) = 100* {1 – [number of missed doses / (number of actual doses + number of missed doses – number of extra doses)]}.

% Compliance (Dialyses) = 100* {1 – [number of missed dialysis visits / (number of actual dialysis visits + number of missed dialysis visits – number of extra dialysis visits)]}.

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

Missed and extra doses/dialysis will be determined as follows:

1. Individual weeks for each subject are examined.
2. Each subject should have 3 doses per week up to Week 12. Anything more will be counted as extra doses; anything less will be counted as missed doses.
3. Subjects who do not complete through Week 12 will be checked for how far they were into the week that they discontinued: 1 or 2 days means that they should have 1 dose; 3 or 4 days = 2 doses; 5 or more days = 3 doses. This will be compared with actual doses for that week to determine missed/extra.
4. The missed and extra doses are then summed across each subject's weeks to get the total missed and extra doses/dialysis.

8. EFFECTIVENESS EVALUATION

8.1 Overview of Effectiveness Analysis Issues

8.1.1 Handling of Dropouts or Missing Data

Missing data will not be imputed. Data from subjects who terminated prematurely will be included in any analyses for which their data is available, unless otherwise specified. Further details on the methodological approaches to handling missing data will be provided in Section 8.2.

8.1.2 Multicenter Studies

Data from all sites will be pooled for the purpose of analyses.

8.1.3 Assessment Time Windows

The assessment time windows in Section 3.1 will be applied to the effectiveness endpoints, unless otherwise specified in the relevant subsections of Section 8.2.

8.1.4 Multiplicity Handling

No adjustments for multiple comparison will be made.

8.2 Effectiveness Variables

Table 1 presents a summary of the study effectiveness variables.

Table 1 Effectiveness Variables

Effectiveness Variables	Summary Statistics
24-hour WI-NRS Score	
Change from baseline in the weekly mean of the 24-hour WI-NRS score to Week 12	X
Percentage of subjects achieving >0, ≥1, ≥2, ≥3, ≥4, ≥5 and ≥6-point improvement from baseline with respect to the weekly mean of the 24-hour WI-NRS at Week 12 (with ≥3- and ≥4- point improvement also reported by region)	X
Sleep Quality Questionnaire	
Change from baseline in the weekly mean of the 24-hour Sleep Quality score to Week 12	X
Percentage of subjects achieving >0, ≥1, ≥2, ≥3, ≥4, ≥5 and ≥6-point improvement from baseline with respect to the weekly mean of the 24-hour Sleep Quality Score at Week 12 (with ≥3- and ≥4- point improvement also reported by region)	X
5-D Itch Scale and Skindex-10 Scale	
Change from baseline in itch-related quality of life to Week 12 as assessed by the 5-D Itch Scale total score and each 5-D Itch Scale individual domain	X
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)	X
EQ-5D-5L-P Questionnaire	
Percentage of subjects with reported problems by level (1 to 5) and EQ-5D-5L dimension at baseline and Week 12	X
Percentage of subjects with no problems (ie, with a level 1 response) by EQ-5D-5L dimension at baseline and Week 12	X
QALY weight at baseline and Week 12	X
Overall Self-Rated Health Status EQ VAS at baseline and at Week 12, along with the change from baseline	X
Subject's health state expressed using the 5 EQ-5D dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression	X
Percentage of subjects with reported problems by level (1 to 5) by EQ-PSO dimension at baseline and Week 12	X
Percentage of subjects with no problems (ie, level 1) by EQ-PSO dimension at baseline and Week 12	X

EQ-5D-5L = 5-level EQ-5D version; EQ-5D-5L-P = EQ-5D-5L with EQ-PSO; EQ-PSO = EQ Pruritus Bolt-on; EQ VAS = EQ visual analogue scale; WI-NRS = Worst Itching Intensity numerical rating scale

This study uses the following 5 instruments to assess effectiveness:

- WI-NRS
- Sleep Quality
- 5D-Itch Scale
- Skindex-10
- EQ-5D-5L-P

The following effectiveness endpoints are derived from these instruments:

- Change from baseline in the weekly mean of the 24 hour WI-NRS score to Week 12
- Percentage of subjects achieving >0, ≥1, ≥2, ≥3, ≥4, ≥5 and ≥6-point improvement from baseline with respect to the weekly mean of the 24-hour WI-NRS at Week 12
- Change from baseline in the weekly mean of the 24-hour Sleep Quality score to Week 12
- Percentage of subjects achieving >0, ≥1, ≥2, ≥3, ≥4, ≥5 and ≥6-point improvement from baseline with respect to the weekly mean of the 24-hour Sleep Quality score at Week 12
- 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 domain score
- 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
- Percentage of subjects with reported problems by level (1 to 5) and by 5-level EQ-5D version (EQ-5D-5L) dimension at baseline and Week 12
- Percentage of subjects with no problems (ie, with a level 1 response) by EQ-5D-5L dimension at baseline and Week 12
- Overall Self-Rated Health Status EQ visual analogue scale (VAS) at baseline and at Week 12, along with the change from baseline
- Subjects' health state expressed using the 5 EQ-5D-5L dimensions
- Percentage of subjects with reported problems by level (1 to 5) and by EQ Pruritus Bolt-on (EQ-PSO) dimension at baseline and Week 12
- Percentage of subjects with no problems (ie, with a level 1 response) by EQ-PSO dimension at baseline and Week 12
- Quality-adjusted life year (QALY) weights using the United States value set

No primary efficacy endpoint will be defined. All effectiveness analyses will be performed on the Safety Population.

8.2.1 WI-NRS Score

Intensity of itch will be measured using the 24-hour WI-NRS (see Appendix 2 of the protocol). Subjects will indicate on a worksheet the intensity of the worst itching they experienced over the past 24 hours by marking 1 of 11 numbers, from 0 to 10, that best

describes the intensity, where "0" is labeled with the anchor phrase "no itching" and "10" is labeled "worst itching imaginable."

The baseline WI-NRS score is defined as the average of the 24-hour WI-NRS scores collected over the Run-in Period, including assessments collected on Day 1 prior to the first dose (see Section 6.2). The Week 12 WI-NRS score is defined as the sum of the WI-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 over the same time period.

WI-NRS scores will be collected on dialysis visits during the Run-in Period, on Day 1, on dialysis visits during Week 12, and on the Early Termination Visit or the End of Treatment Visit. A subject is expected to have 3 dialysis visits a week; therefore, a total of 4 scores are expected to contribute to each of the baseline WI-NRS score and the Week 12 WI-NRS score. WI-NRS scores collected at the Early Termination Visit or unscheduled visits will contribute to the Week 12 WI-NRS Score if collected from Day 76 to Day 86, inclusive. WI-NRS scores collected at unscheduled visits during the Run-in Period will be assigned to the nearest planned visit. If >4 scores are collected in each of these respective time periods, the extra score(s) will be factored into the calculation of the baseline WI-NRS score or the Week 12 WI-NRS score, as applicable.

If the WI-NRS scores are missing for >2 dialysis visits during the collection period on Week 12 through the first dialysis visit of Week 13, then the Week 12 WI-NRS score will be set to missing. If a subject terminates treatment prematurely, but has at least 1 non-missing scores collected during that period, the Week 12 WI-NRS score will not be set to missing.

According to the protocol, the subject must have ≥3 non-missing WI-NRS scores from the start of the Run-in Period up to and including the assessment on Day 1 to be eligible for the study (ie, at most 1 score may be missing). Regardless, a subject's baseline WI-NRS score will only be set to missing if the subject is missing >2 scores collected during this baseline collection period.

Summary statistics (n, mean, standard deviation, minimum, maximum) for the baseline WI-NRS score and the Week 12 WI-NRS score will be produced, along with the change from baseline. Missing values will not be imputed.

The count and percentage of subjects who have an improvement from baseline of >0, ≥1, ≥2, ≥3, ≥4, ≥5 and ≥6 points at Week 12 will be reported. The count and percentage of subjects with an improvement from baseline of ≥3 and ≥4 points at Week 12 will also be reported by region. A figure presenting the percentages of subjects who have an improvement from baseline of >0, ≥1, ≥2, ≥3, ≥4, ≥5 and ≥6 points at Week 12 will also be prepared.

Individual WI-NRS scores will be presented in a by-subject listing.

It is important to note that, in patients undergoing hemodialysis, 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) may actually be collected in part or in whole during the first day of the next week (eg, Week 13).

8.2.2 Sleep Quality Questionnaire

The impact of itch on subjects' quality of sleep will be measured using the Sleep Quality Questionnaire which utilizes a numeric rating scale (see Appendix 3 of the protocol). Subjects will indicate on a worksheet how their itch interferes with their sleep over the past 24 hours by marking 1 of 11 numbers, from 0 to 10, that best describes the interference, where "0" is labeled with the anchor phrase "did not interfere" and "10" is labeled "completely interfered."

The baseline Sleep Quality score is defined as the average of the Sleep Quality scores collected over the Run-in Period, including assessments collected on Day 1 prior to the first dose. The Week 12 Sleep Quality score is defined as the sum of the Sleep Quality 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 over the same time period.

The Sleep Quality Questionnaire will be administered on the same days as the WI-NRS (see Section 8.2.1). The same rules as in Section 8.2.1 for missing and extra scores will be applied to the management of Sleep Quality scores.

Summary statistics (n, mean, standard deviation, minimum, maximum) for the baseline Sleep Quality score and the Week 12 Sleep Quality score will be produced, along with the change from baseline.

The percentages of subjects who have an improvement from baseline of >0, ≥1, ≥2, ≥3, ≥4, ≥5 and ≥6 points at Week 12 will be analyzed and presented in the same manner as that for the WI-NRS scores presented in Section 8.2.1. The count and percentage of subjects with an improvement from baseline of ≥3 and ≥4 points at Week 12 will also be reported by region.

Individual Sleep Quality scores will be presented in a by-subject listing.

8.2.3 5D-Itch Scale

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

The duration, degree, and direction domains each include 1 item, while the disability domain has 4 items. All items of the first 4 domains were measured on a 5-point Likert scale. The distribution domain includes 16 potential locations of itch, including 15 body part items and 1 point of contact with clothing or bandages. Single-item domain scores

(duration, degree, and direction) are equal to the value indicated below the response choice (range 1–5). The disability domain includes 4 items that assess the impact of itching on daily activities: sleep, leisure/social activities, housework/errands, and work/school. The score for the disability domain is achieved by taking the highest score on any of the 4 items. For the distribution domain, the number of affected body parts is tallied (potential sum 0–16), and the sum is sorted into 5 scoring bins: sum of 0–2 = score of 1, sum of 3–5 = score of 2, sum of 6–10 = score of 3, sum of 11–13 = score of 4, and sum of 14–16 = score of 5. The scores of each of the 5 domains are achieved separately and then summed together to obtain a total 5-D score. 5-D scores can potentially range between 5 (no pruritus) and 25 (most severe pruritus).

Total 5-D Itch Scale score = duration score (single item) + degree score (single item) + duration score (single item) + maximum (4 disability items) + category score based on sum of affected body parts.

The scoring manual does not give specific direction regarding scoring when some questions are missing; therefore, each domain and the total score will be set to missing when any of their individual components are missing, with the exception of the disability domain. The maximum of any items present for disability will be used for that domain.

5-D Itch Scale questionnaires should be completed at the first dialysis visit of Week 1 (for the baseline scores) and the first dialysis visit after the last dose of CR845 (for the Week 12 scores). For the total 5-D Itch Scale score and each respective domain score, the Week 12 score would come from the Week 13 End of Treatment visit if non-missing; otherwise, it would come from an unscheduled visit or Early Termination Visit collected from Day 82 to Day 86, inclusive.

For the total 5-D Itch Scale score and each domain score, summary statistics (n, mean, standard deviation, minimum, maximum) for the respective baseline and Week 12 score will be produced, along with the change from baseline. Missing scores will not be imputed.

Individual scores will be presented in a by-subject listing.

8.2.4 Skindex-10

Developed specifically for uremic pruritus, the Skindex-10 (see Appendix 4 of the protocol) is an instrument for measurement of quality of life. Subjects are asked the question “During the past week, how often have you been bothered by” and respond by filling in 1 of 7 circles numbered from 0 (labeled with the anchor phrase “never bothered”) to 6 (labeled as “always bothered”) for each of the 10 questions.

The total score is the sum of the numeric value of each answered question. The total score is subdivided into 3 domain scores, which are sums of the scores of the following questions: disease domain (questions 1 to 3), mood/emotional distress domain (questions 4 to 6), and social functioning domain (questions 7 to 10).

Skindex-10 questionnaires should be completed on the same days as the 5-D Itch Scale questionnaires (see Section 8.2.3).

The scoring manual for the Skindex-10 does not give specific direction regarding scoring when some questions are missing; therefore, the 3 domains and the total score will be set to missing when any of their individual components are missing. Otherwise, the same rules for missing and extra questionnaires in Section 8.2.3 apply to the Skindex-10.

The same summary statistics presented in Section 8.2.3 for the 5-D Itch Scale scores will be applied to and reported for the Skindex-10 scores, both for the total score and each domain. Missing scores will not be imputed.

Individual scores will be presented in a by-subject listing.

8.2.5 EQ-5D-5L-P

The EQ-5D-5L-P questionnaire consists of 3 component parts: the EQ-5D descriptive system, the EQ VAS, and the EQ-PSO. The EQ-5D descriptive system and the EQ VAS make up the EQ-5D-5L questionnaire, which was introduced by the EuroQol Group in 2009. The EQ-PSO is a 2-dimension questionnaire that was added on to the EQ-5D-5L. (See Appendix 6 of the protocol.)

All 3 questionnaires measure the subject's perceived state of health as of the day the test is taken. Only descriptive analyses will be conducted for these scores.

The 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. The baseline value for each of the 3 component parts (and dimension, in the case of the EQ-5D descriptive system and the EQ-PSO) would come from the third dialysis visit of the Run-In Period if non-missing. Similarly, the Week 12 value for each component part or dimension would come from third dialysis visit of Week 12 if non-missing. Otherwise, questionnaires collected at the Early Termination Visit or unscheduled visits will contribute to the Week 12 value if collected from Day 79 to Day 83, inclusive.

8.2.5.1 EQ-5D Descriptive System

The EQ-5D descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels that can be coded as single-digit numbers ranging from 1 to 5 (indicated parenthetically): no problems (1), slight problems (2), moderate problems (3), severe problems (4) and extreme problems (5).

These coded numbers can be reported as 5-digit codes corresponding to the 5 dimensions in the following order: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The code ranges between no problems on all 5 dimensions (11111) to extreme problems on all 5 dimensions (55555). Missing values for specific

dimensions will be coded as 9, unless the entire EQ-5D descriptive system questionnaire is missing, in which case the 5-digit code will be missing.

For each of the 5 dimensions, the number and percentage of subjects with each reported level (1 to 5) will be tabulated for baseline and Week 12. Also, the count and percentage of subjects with no problems (ie, level 1) and with problems (ie, levels 2 to 5) by EQ-5D-5L dimension will be separately summarized for baseline and Week 12. Histograms will be created for the percentage of responses by level of severity for EQ-5D-5L dimensions at baseline and at Week 12.

The Euroqol Group developed a EQ-5D-5L Crosswalk Index Value Calculator that maps the 5-digit codes to QALY weights that range in value from 0 to 1. Although the crosswalk provides values for 6 countries, only values presented in the crosswalk for the United States will be used for this study. Each subject's 5-digit codes will be mapped by referencing the crosswalk available on the Euroqol Group's website (see hyperlink in Section 14). Summary statistics (n, mean, standard deviation, minimum, maximum) for the baseline and Week 12 QALY weights will be produced, along with change from baseline.

A listing will be created that displays the subjects' 5-digits codes and associated QALY weights.

8.2.5.2 EQ VAS

The EQ VAS records the subject's self-rated health on a vertical visual analogue scale, with values ranging from 0 ("The worst health you can imagine") to 100 ("The best health you can imagine").

A summary table for EQ VAS will include descriptive statistics (number of subjects, mean, standard deviation, median, minimum, maximum, 25th percentile, and 75th percentile) for the baseline and Week 12 values, along with the change from baseline.

Individual scores will be presented in a by-subject listing.

8.2.5.3 EQ-PSO

The EQ-PSO will be added to the EQ-5D-5L and includes 2 additional dimensions "skin irritation" and "self-confidence" to better capture the itch-associated burdens [Swinburn 2013]. Like the EQ-5D descriptive system, each dimension has 5 levels of severity ranging from 1 to 5. The levels for the itching dimension are as follows: no itching (1), slight itching (2), moderate itching (3), severe itching (4), and extreme itching (5). The levels for the self-confidence dimension are as follows: no problems with self-confidence (1), slight problems with self-confidence (2), moderate problems with self-confidence (3), severe problems with self-confidence (4), and extreme problems with self-confidence (5).

For each of the 2 dimensions, the number and percentage of subjects with each reported level (1 to 5) will be tabulated for baseline and Week 12. Subjects with missing values at

baseline will still be included in the Week 12 summary, and subjects with missing values at Week 12 will still be included in the baseline summary.

Also, the number and percentage of subjects with no problems (ie, with a level 1 response) by dimension will be summarized for baseline and Week 12 in a separate table.

These coded numbers will be reported as 2-digit codes in the same manner as that of the EQ-5D descriptive system, in the order of "skin irritation" followed by "self-confidence." A listing will be created that displays the subjects' 2-digit codes.

9. SAFETY EVALUATION

9.1 Overview of Safety Analysis Methods

The following assessments will be used to evaluate the safety of CR845 in hemodialysis subjects with moderate-to-severe pruritus:

- Adverse events
- Clinical laboratory parameters
- Vital signs
- 12-lead ECG

Analysis of all safety data collected during the Treatment Period will be performed on the Safety Population. Any analysis of safety data collected during the Screening Period will be performed on the Enrolled Population.

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.

9.2 Adverse Events

The period of adverse event reporting will start after the signing of the informed consent form through the Follow-up Visit, or Early Termination Visit if the Follow-up Visit was not conducted, or 7 days after the last dose if the Early Termination Visit and Follow-up Visit were both missing. All adverse events that occur during this reporting period will be collected for all subjects, including subjects who are deemed to be screen failures. All tabular adverse event summaries will be for treatment-emergent adverse events (TEAEs) relative to the Treatment Period, unless otherwise specified. Treatment-emergent adverse events are defined as those adverse event that start any time after the first dose of study drug up to the Follow-up Visit or Early Termination Visit (or 7 days after the last dose if no Early Termination Visit was conducted), whichever is later.

For events with missing start dates, the following criteria will be used:

- If the start date for a particular event is missing, then the event is considered treatment emergent.
- If the start time is missing and the start date is the same as the first dosing date, then the event is considered treatment emergent.

If it cannot be determined whether or not an event is treatment emergent due to a missing or partial date, then the event will be assumed to be treatment emergent.

All adverse events will be coded to SOC and preferred term using MedDRA version 22.0. MedDRA will be used to map adverse events verbatim to SOC and preferred term for standardization and summary purposes.

The incidence of TEAEs will be summarized. If a subject experienced more than 1 episode of an adverse event, the subject will be counted once for that preferred term. If

a subject had more than 1 adverse event in a SOC, the subject will be counted only once in that SOC. The summary tables will include the incidences of SOCs, as well as the incidences of preferred terms within each SOC. Incidence for SOC will be presented by decreasing frequency overall and then alphabetically, and for preferred term within each SOC, by decreasing frequency overall and then alphabetically.

The investigator is to record the severity of each adverse event as mild, moderate, or severe. If the same TEAE occurs for a subject on multiple occasions, the TEAE will be categorized according to the highest severity rating for that TEAE in that subject. If the severity of the TEAE is not reported, then the severity of the TEAE will be counted as severe. The incidence within each category will be presented.

The investigator is to record their opinion on the relationship of each adverse event to study drug (not related and related). If a subject experiences the same adverse event multiple times, the event with the strongest relationship to study drug will be counted. The incidence within each category will be presented. For the summary of TEAEs by relationship to study drug, if the relationship is missing, it will be counted as related.

Separate tables summarizing the incidence of adverse events of special interest (AESIs) be presented for the Treatment Period. Selected preferred terms shown in Appendix 15.3 are combined into the following categories:

- Gait disturbance
- Fall
- Dizziness
- Somnolence
- Seizure
- Syncope
- Mental status changes
- Mood changes
- Unusual feeling, sensation
- Tachycardia
- Palpitation

To explore the duration and temporal relationship of treatment-emergent AESIs, a graphical representation of occurrences and durations of adverse events within each AESI will be presented with subjects on the y-axis and time on the x-axis (Swimmer plot).

The incidence of infections related to uremic pruritus based on adverse events, hospitalizations, and/or use of antibiotics for treatment of infection related to uremic pruritus will be also be reported with counts and percentages. The incidence of all infections will be summarized by preferred term.

The following summary tables will be presented for the Safety Population:

- An overall summary showing the number and percentage of subjects with a(n) TEAE, serious TEAE, adverse events resulting in death (regardless of treatment emergence), related TEAE, related serious TEAE, severe TEAE, TEAE leading to dose interruption, TEAE leading to study drug discontinuation, and TEAE of special interest. This table will also include number of events. This display will be repeated for subgroups by region.
- Incidence of TEAEs by SOC and preferred term
- Incidence of serious TEAEs by SOC and preferred term
- Incidence of related TEAEs by SOC and preferred term
- Incidence of TEAEs by SOC, preferred term, and maximum severity
- Incidence of TEAEs leading to study drug discontinuation by SOC and preferred term
- TEAEs by region, SOC, and preferred term
- Incidence of most common TEAEs (2% or more of subjects) by preferred term
- Incidence of treatment-emergent AESIs by preferred term
- Incidence of TEAEs categorized based on custom MedDRA query (CMQ) events
- Incidence of infections by preferred term
- Incidence of infections potentially related to uremic pruritus by preferred term, where infections are deemed "potentially related to uremic pruritus" based on adverse events, hospitalizations, and/or use of antibiotics.

The incidence of TEAEs in each CMQ category (see Appendix 15.2) will be summarized. If a subject experienced more than 1 episode of an adverse event, the subject is counted once for that preferred term; the total number of subjects reporting an event in the category will also be reported.

In addition, all adverse events for each subject will be listed in chronological order including subject identifier, age, race, gender, a flag indicating whether the event was treatment-emergent, and all related event status information (start and stop dates, whether the event was ongoing, study day of onset, severity, seriousness, relationship to study drug, action taken with study drug, and outcome). Note: For the all adverse event listing only, any screen failure subject who has an adverse event after signing the informed consent form will be included for completeness. Separate listings will be generated for serious adverse events (SAEs), deaths, adverse events leading to treatment discontinuation, and adverse events of special interest. Additionally, a coding list of preferred terms and the verbatim text associated with them will be produced.

No statistical tests will be performed on adverse events.

9.3 Deaths, Serious Adverse Events, and Other Significant Adverse Events

An SAE is defined as any adverse event occurring at any dose and regardless of causality that results in death, is life threatening, requires in-patient hospitalization or prolongation

of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or is an important medical event.

Serious adverse events will be collected from date the informed consent form is signed up to the Follow-up Visit or 7 days following the last dose of study drug, whichever is later. Serious adverse events that occur up to 30 days after the last dose of study drug should also be documented on an SAE form if they are deemed by the investigator to be "related" to the study drug. Serious adverse events that occur after the Follow-up Visit or 30 days after the last dose of study drug, whichever is later, do not need to be documented on an SAE form if they are deemed by the investigator to be "not related" to study drug or the conduct of the study. A more detailed definition of SAEs is provided in Protocol Section 6.5.3.1.

Subject deaths are captured on the *Adverse Events* CRF page. Subject death listings will include all death data available including date of death and cause of death. Additionally, SAEs and adverse events resulting in study drug discontinuation will be listed.

9.4 Clinical Laboratory Evaluation

Blood samples will be collected during screening, on Day 1 and at End of Treatment/Early Termination. Summaries of actual values and the changes from baseline to each time point (when applicable) and the last post-baseline treatment visit will be presented for quantitative laboratory parameters (eg, white blood cell count, lymphocyte count). Only data from the central laboratory will be used. The last post-baseline treatment visit will be latest value recorded for a given parameter, not including the Follow-up Visit and unscheduled visits following the End of Treatment/Early Termination Visit.

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 the assessment is performed prior to dosing.

All laboratory evaluation summaries will include the subjects in the Safety Population who have at least 1 post-baseline time point (for criteria based on post-baseline assessments) and with both a baseline and at least 1 post-baseline time point (for criteria evaluating changes from baseline).

Laboratory values will be reported in Système International units, unless otherwise specified.

Laboratory test results will be classified according to whether the value was below (L), within (N), or above (H) the laboratory parameter reference range. A summary of treatment-emergent shifts will compare the baseline L/N/H classification for each laboratory test to the highest and/or lowest L/N/H classification during the Treatment Period.

Additionally, alanine aminotransferase, aspartate aminotransferase, bilirubin, and alkaline phosphatase will be presented in a separate table with: 3× and 5× upper limit of normal (ULN) flagged for alanine aminotransferase and aspartate aminotransferase; 2×ULN flagged for bilirubin, and 1.5×ULN flagged for alkaline phosphatase. Additionally, subjects that have alanine aminotransferase or aspartate aminotransferase >3×ULN and total bilirubin >2×ULN will be flagged as potential Hy's Law cases and summarized. These liver function values will be presented in a separate listing with 3× and 5×ULN flagged for alanine aminotransferase and aspartate aminotransferase; 2×ULN flagged for total bilirubin; and 1.5×ULN flagged for alkaline phosphatase.

Additionally, clinically significant shifts from baseline for hemoglobin, calcium, serum albumin, phosphate, and potassium will be reported. Ranges are given below.

Test	Low	High
Hemoglobin (g/dL)	<7	>14
Calcium (mg/dL)	<7	>10.5
Serum albumin (g/dL)	<3	>5.5
Phosphate (mg/dL)	<2.5	>8
Potassium (mmol/L)	<2.5	>7

All clinical laboratory values will be presented in a listing.

9.5 Vital Signs, Physical Findings, and Other Observations Related to Safety

9.5.1 Vital Signs

Vital signs (including body temperature, heart rate, and systolic and diastolic blood pressure) will be collected prior to dialysis during screening; at the third dialysis session of Weeks 1, 5, 9; at the End of Treatment Visit or Early Termination Visit; and at the Follow-up Visit. Heart rate will be collected at each dialysis visit; if clinically significant and outside the pre-specified visits mentioned above, the heart rate will be recorded on the relevant CRF page. Dry body weight will be collected during screening

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 given that the assessment is performed prior to dosing.

Summary tables will include descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum) for baseline and each post-baseline assessment and the last post-baseline treatment visit. Descriptive statistics will be calculated on both the actual value and the change from baseline score. The last post-baseline treatment visit will be latest value recorded for a given parameter, not including the Follow-up Visit and unscheduled visits following the End of Treatment/Early Termination Visit.

All vital sign summaries (including the analysis of clinically notable values below) will include the subjects in the Safety Population who have at least a post-baseline assessment (for criteria based on post-baseline assessments) and subjects who have both a baseline and at least 1 post-baseline assessment (for criteria evaluating changes from baseline).

Clinically notable vital signs will be identified based on the criteria below. For each vital sign parameter, the number and percentage of subjects with at least 1 notable value will be tabulated by week and overall for the Treatment Period.

Vital Sign Parameter	**Value**
Systolic blood pressure	≥180 mm Hg ≤90 mm Hg
Diastolic blood pressure	≥100 mm Hg ≤60 mm Hg
Heart rate	>130 beats per minute <55 beats per minute

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

9.5.2 12-Lead Electrocardiograms

Standard 12-lead ECGs will be performed prior to dialysis during screening and at End of Treatment/Early Termination.

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, including the last post-baseline treatment visit. The last post-baseline treatment visit will be latest value recorded, not including unscheduled visits following the End of Treatment/Early Termination. The worst post-baseline result across all visits will be flagged and reported separately; this may include measurements that were not in the individual visit summaries.

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.

10. OTHER ANALYSES

10.1 Hospitalizations, Emergency Department Encounters

The count and percentage of subjects who were hospitalized as in-patients, the count and percentage of subjects who underwent dialysis during hospitalization, and summary statistics for duration of hospital stay will be reported. In addition, a listing will be generated that includes the date of admission, date and time of discharge, reason for hospitalization, the total number of dialysis procedures completed during the hospital stay, whether the subject received any medications administered or had a procedure during the hospital stay, and whether the subject had any other medical conditions noted during the hospital stay.

A parallel summary and listing will also be created for emergency room visits.

10.2 Missed Dialysis Visits and Incidence of Infection

The analysis of missed dialysis visits is described in Section 7, Measurements of Treatment Compliance. The analysis of incidence of infection is described in Section 9.2, Adverse Events.

11. INTERIM ANALYSES AND DATA MONITORING

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

12. CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL

All changes below are in reference to version 2.0 (12FEB2019) of the protocol

- The protocol states that approximately 400 subjects will be enrolled at approximately 80 sites, while Section 2.6 of this SAP states that approximately 200 subjects will be enrolled at approximately 50 clinical sites.

- Effectiveness analyses will be performed on the Safety Population rather than on the Full Analysis Population as defined in the protocol. Main and ancillary analyses as described in Section 6.4 of the protocol will not be performed.

- The incidence of AESIs will not be presented for the Run-In Period.

- "Most common TEAEs" will be defined as 2% or more of subjects rather than 5% or more.

- The derivation and analyses of EQ-5D-5L QALY weights were added.

- The percentage of subjects achieving >0, ≥1, ≥2, ≥3, ≥4, ≥5 and ≥6-point improvement from baseline with respect to the Sleep Quality score and the WI-NRS score at Week 12 are reported, while the protocol only specifies the percentage of subjects achieving >0, ≥1, ≥2, ≥3, and ≥4-point improvement from baseline with respect to the WI-NRS score at Week 12

- The protocol included analysis of covariance (ANCOVA) analyses of continuous efficacy variables, however, with only the baseline as a covariate, the model least squares mean yields the same value as the raw mean.

- The protocol included logistic regression for dichotomous efficacy variables, however, with a single treatment group, there are no meaningful odds ratios to be reported.

13. STATISTICAL APPENDIX

Not applicable.

14. REFERENCES

Swinburn P, Lloyd A, et al. Development of a Disease-Specific Version of the EQ-5D-5L for Use in Patients Suffering from Psoriasis: Lessons Learned from a Feasibility Study in the UK. Value in Health. 2013;16:1156-62

https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/valuation-standard-value-sets/crosswalk-index-value-calculator/ [downloaded November 2019]

15. APPENDICES

15.1 Schedule of Events

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 Week 12 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								

CRF = case report form; ECG = electrocardiogram; EOT = end of treatment; EQ-5D-5L-P = EQ-5D-5L with EQ-PSO bolt-on; IV = intravenous; PRO = patient reported outcome; WI-NRS=Worst Itching Intensity numeric response scale

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

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 WI-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. WI-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 WI-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

Source: Table 2, Schedule of Events, of the CR845-CLIN3105 protocol.

15.2 Custom MedDRA Query (CMQ) Categories and Preferred Terms

CMQs

Gait Disturbance
- Ataxia
- Balance disorder
- Coordination abnormal
- Gait disturbance
- Gait inability
- Tandem gait test abnormal

Dizziness
- Dizziness
- Dizziness Postural
- Vertigo

Syncope
- Presyncope
- Syncope

Fall & Potentially Drug Related Injury
- Accident
- Back injury
- Contusion
- Fall
- Fracture (all preferred terms containing “fracture”)
- Head injury
- Injury
- Limb injury
- Muscle contusion
- Muscle injury
- Road traffic accident
- Skeletal injury
- Haematoma
- Subdural hematoma
- Epidural haematoma
- Traumatic haematoma
- Periorbital haematoma
- Ecchymosis
- Subdural hematoma
- Subdural haemorrhage

Mood Changes & Behavioral Changes
- Abnormal behavior

Affect lability
Aggression
Agitation
Anger
Anxiety
Apathy
Blunted affect
Crying
Depressed mood
Disinhibition
Dysphoria
Emotional distress
Emotional poverty
Euphoric mood
Flat affect

Grandiosity
Hostility
Inappropriate affect

Listless
Mood altered
Mood swings
Morose
Nervousness
Patient uncooperative
Restlessness
Social avoidant behavior

Seizures

Autonomic seizure
Clonic convulsion
Drug withdrawal convulsions
Epilepsy
Epileptic aura
Focal dyscognitive seizures
Generalised tonic-clonic seizure
Partial seizures
Partial seizures with secondary generalisation

Seizure
Seizure cluster
Simple partial seizures
Status epilepticus
Tonic convulsion

Mental Status & Cognitive Changes
- Acute psychosis
- Delirium
- Altered state of consciousness
- Hallucination (any preferred term containing "Hallucination")
- Bradyphrenia
- Change in sustained attention
- Cognitive disorder
- Confusional state
- Delusion (any preferred term containing "Delusion")
- Depressed level of consciousness
- Disorientation
- Encephalopathy
- Illusion
- Judgment impaired
- Lethargy
- Mental impairment
- Mental status changes
- Stupor
- Thinking abnormal

Unusual Feeling, Sensation
- Asthenia
- Depersonalisation/derealisation disorder
- Derealisation
- Dissociation
- Feeling abnormal
- Feeling cold
- Feeling despair
- Feeling drunk
- Feeling guilty
- Feeling hot
- Feeling jittery
- Feeling of body temperature change
- Feeling of despair
- Feeling of relaxation
- Feelings of worthlessness
- Malaise
- Psychiatric symptom
- Sensation of foreign body
- Suffocation feeling

Palpitations & Tachychardia
- Palpitations
- Heart rate irregular
- Heart rate increased

Tachycardia
Atrial tachycardia
Junctional ectopic tachycardia
Supraventricular tachycardia
Ventricular tachycardia
Sinus tachycardia
Tachycardia paroxysmal
Tachyarrhythmia
Ventricular tachyarrhythmia

Somnolence
Somnolence
Sleep disorder
Abnormal sleep related event
Microsleep
Sleep attacks
Sedation

15.3 Treatment-emergent Adverse Events of Special Interest and Preferred Terms

TEAE of Special Interest Terms	**Preferred Terms**
Gait disturbance	Gait disturbance
Falls	Fall
Dizziness	Dizziness
Somnolence	Somnolence
Seizures	Seizure
Syncope	Syncope
Mental status changes	Mental status changes
Mood changes	Mood altered
Unusual feeling/sensation	Feeling abnormal
Tachycardia	Sinus tachycardia, Tachycardia, Tachyarrhythmia
Palpitation	Palpitations

TEAE = treatment emergent adverse event