STATISTICAL ANALYSIS PLAN
09 March 2020 Final v1.1

AN OPEN-LABEL, MULTICENTER, EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY OF INTRAVENOUS CR845 IN HEMODIALYSIS PATIENTS WITH CHRONIC KIDNEY DISEASE-ASSOCIATED PRURITUS

PROTOCOL NUMBER CR845-CLIN3101

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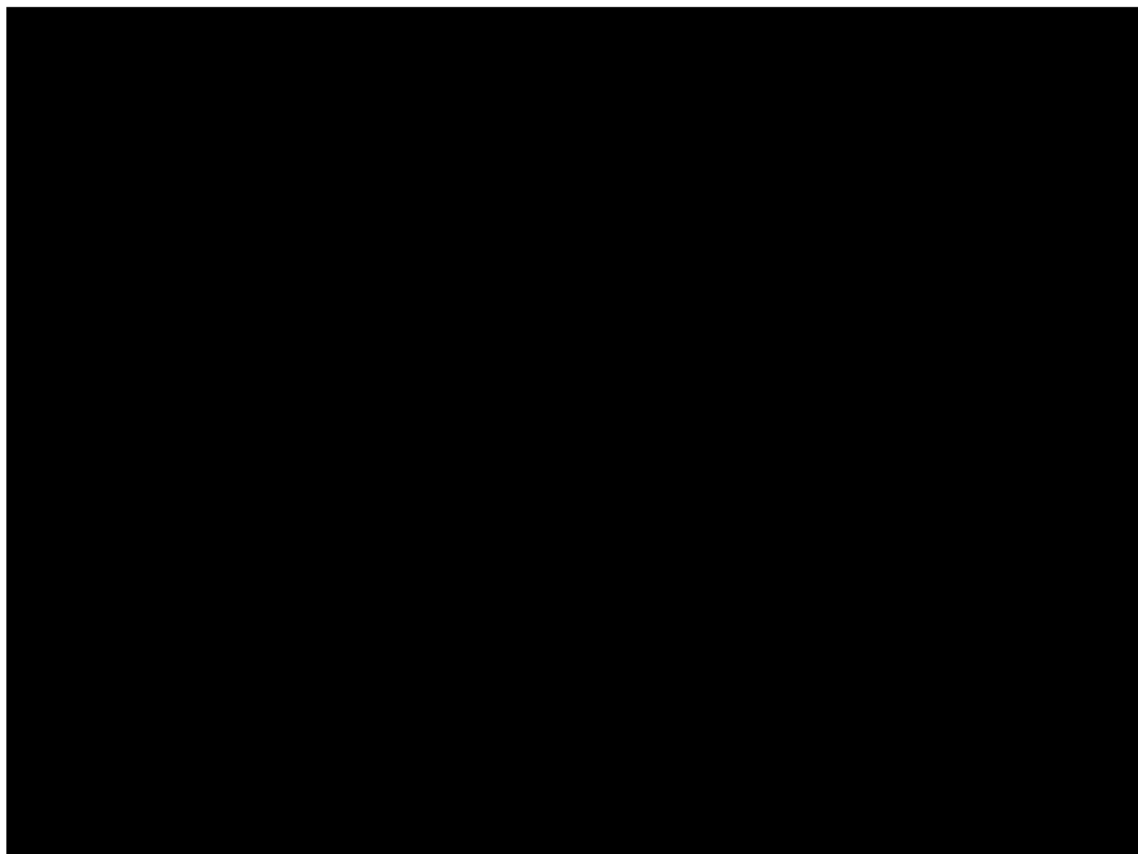Telephone: (919) 408-8000
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DOCUMENT VERSION CONTROL

Version Number	Date	Comments/Changes
1.0	19 September 2019	
1.1	09 March 2020	• SMQ and K-M analyses removed • Correction to potassium normal range and hemoglobin units • Minor edits and clarifications

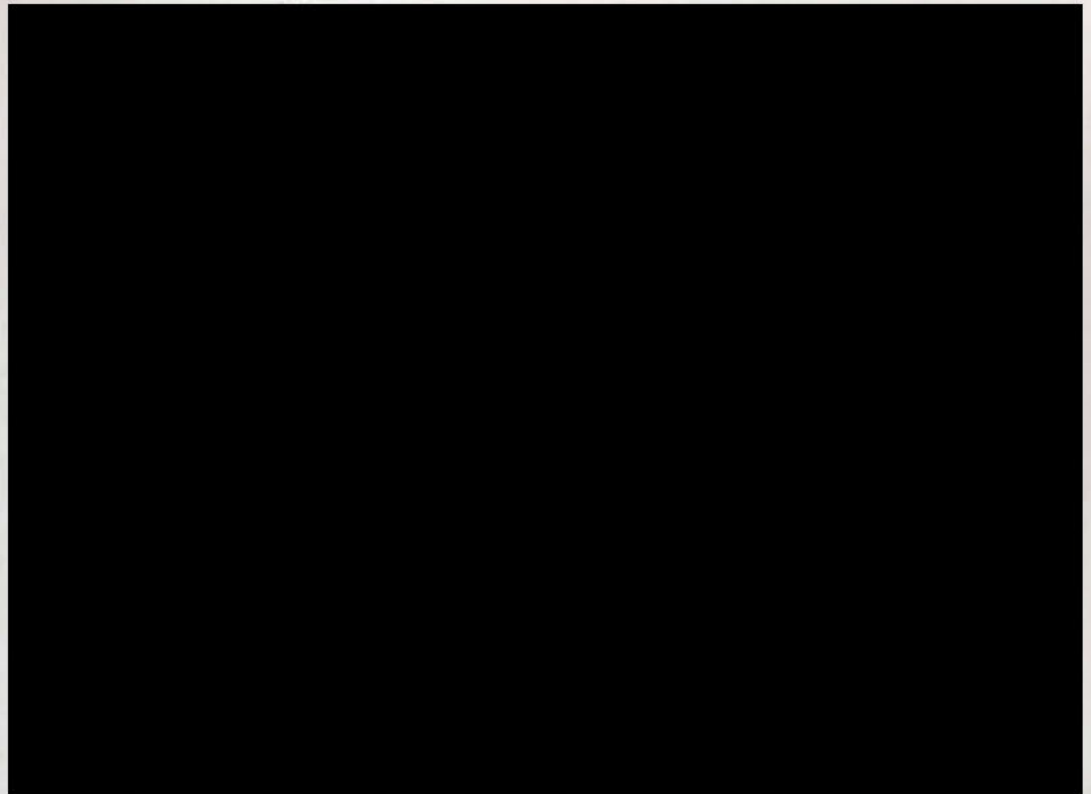## APPROVALS

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Definition
CMQ	Custom MedDRA Query
CRF	case report form
CSR	Clinical Study Report
ECG	electrocardiogram
ESA	erythropoiesis-stimulating agent
ESRD	end-stage renal disease
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
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
TEAE	treatment-emergent adverse event

1.   PURPOSE OF THE ANALYSES

CR845-CLIN3101 is an open-label, multicenter, long-term safety study (both as an extension to prior protocols and with de novo subjects) to evaluate the safety of intravenous (IV) CR845 in hemodialysis subjects with Chronic Kidney Disease-associated pruritus. Treatment of IV CR845 at a dose of 0.5 mcg/kg is administered after each dialysis session over a Treatment Period of up to 52 weeks. This study is sponsored by Cara Therapeutics, Inc.

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-CLIN3101 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 (CSR).

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 administered after each dialysis session over a Treatment Period of up to 52 weeks in hemodialysis subjects who previously participated in the phase 2 studies CR845-CLIN2005 (Part B) or CR845-CLIN2101 (Part A) and in hemodialysis subjects who had not been previously exposed to CR845 and did not previously participate in the phase 2 studies CR845-CLIN2005 (Part B) or CR845-CLIN2101 (Part A) (de novo subjects).

2.2 Overall Study Design and Plan

This is a multicenter, open-label, phase 3 study to evaluate the long-term safety of IV CR845, administered after each dialysis session for up to 52 weeks in subjects who participated in CR845-CLIN2005 (Part B) or CR845-CLIN2101 (Part A) and in de novo hemodialysis subjects who had not been previously exposed to CR845 and were not part of the phase 2 clinical studies CR845-CLIN2005 (Part B) or CR845-CLIN2101 (Part A). This study will consist of a Screening Visit, a 52-week study drug Dosing Period, an End of Treatment Visit, and a Follow-up Visit. All subjects will have a Screening Visit, which can be performed anytime within 14 days prior to the first dose of study drug, to confirm eligibility.

Day 1 of the Treatment Period will be defined as the day of administration of the first dose of study drug. Each subject will receive CR845 at a dose of 0.5 mcg/kg after each dialysis session, 3 times per week for up to 52 weeks and approximately 156 doses of study drug. All scheduled study visits during the Treatment Period will be conducted on dialysis days.

Clinical laboratory tests, electrocardiograms (ECGs), vital signs, adverse events, and concomitant medications will be monitored throughout the study. Blood samples for inflammatory biomarkers will be collected from all subjects prior to dialysis on Day 1 and periodically until the End of Treatment or Early Termination Visit, per the schedule of events (Appendix 15.1). Blood samples will also be collected periodically for clinical laboratory tests.

The number of and reason(s) for missed dialysis will be recorded throughout the study. Incidence of infection, hospitalizations, emergency department encounters or observation stays, and/or use of antibiotics will also be recorded, with reason for infection if available. Iron and erythropoiesis-stimulating agent (ESA) use will be recorded throughout the study.

The last dose of study drug will be administered at the last dialysis visit on Week 52, or at early termination. The End of Treatment Visit 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:
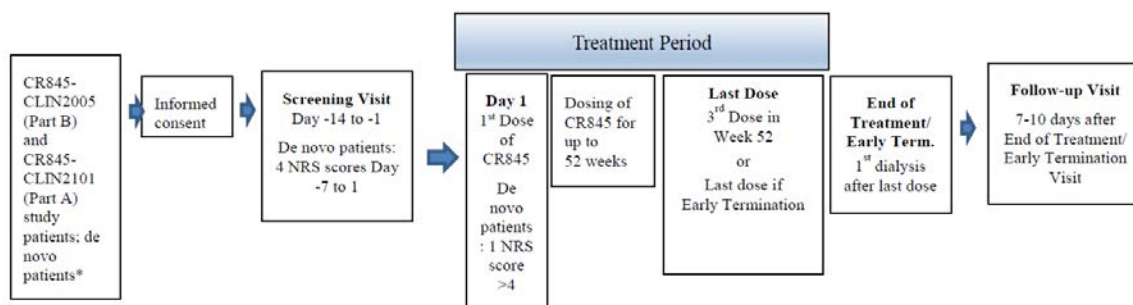
*de novo patients: not previously exposed to CR845 and not previously enrolled in CR845-CLIN2005 (Part B) and CR845-CLIN2101 (Part A)

2.3   Study Population

The study population includes males and females 18 years of age or older who either participated in CR845-CLIN2005 (Part B) or CR845-CLIN2101 (Part A) or are de novo subjects. All subjects must currently be on hemodialysis for end-stage renal disease (ESRD). Subjects who previously participated in CR845-CLIN2005 (Part B) or CR845-CLIN2101 (Part A) must have been categorized as experiencing moderate to severe uremic pruritus in those studies and must have continued to experience chronic kidney disease-associated pruritus since the study. De novo subjects must be experiencing chronic kidney disease-associated pruritus at the time of screening. A full list of inclusion and exclusion criteria may be found in Section 6.2 of the protocol.

Subjects providing informed consent will be screened for inclusion in the study before enrollment and dosing; all eligibility criteria must be met before a subject is enrolled. No waivers of entry criteria will be approved for this study. Rescreening will be considered on an individual subject basis and must first be approved by the Sponsor or Medical Monitor.

2.4   Treatment Regimens

All subjects will receive 0.5 mcg/kg CR845 as a single IV bolus 3 times a week immediately after each dialysis session for up to 52 weeks.

2.5   Treatment Group Assignments or Randomization

As this is an open-label, single-treatment study, all subjects will be assigned to a dose of 0.5 mcg/kg, and no randomization will occur. As described below in section 3, results will be displayed by the treatment received previously (or de novo), thus "treatment group" will be used throughout this document to refer to those groupings.

2.6   Sample Size Determination

Up to 300 male and female hemodialysis subjects who previously participated in either CR845-CLIN2005 (Part B) or CR845-CLIN2101 (Part A) or are de novo subjects will be enrolled in this study at up to 35 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.

Unless otherwise specified, all displays will summarize results by the following groups:

- All Doses CR845 Treated from Previous Studies
- Placebo Treated from Previous Studies
- De Novo
- All Subjects

Note that the previous studies included multiple dose levels for CR845; these subjects will not be displayed separately in the analyses for this protocol; all dose levels will be pooled for the active subjects from the previous studies. Additionally, only data collected under this protocol will be displayed in these analyses.

<u>For categorical variables</u>, 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%) where the percentage is 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 analysis population for the treatment group will be the denominator.

<u>For continuous variables</u>, 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 digit 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.

<u>No tests of hypothesis of treatment group differences are planned</u>; 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, the baseline value will be considered the last non-missing measurement observed prior to the first dose of study drug in the current protocol.

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

Data will be listed by treatment in the preceding study (see above) or de novo status, and by subject. 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 the safety population unless specified otherwise (e.g. screen failure listing, disposition listing).

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

Subject identifiers presented in the listings are the identifiers assigned in the current study, CR845-CLIN3101.

4. ANALYSIS POPULATIONS

The Safety Population will be used for all analyses; this will include all enrolled patients who received at least 1 dose of study drug.

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 reason for treatment discontinuation, will be presented for subjects from the previous studies (by treatment), de novo subjects, and overall. Subjects completing follow-up will also be presented. The number of subjects included the Safety Population will also be tabulated.

The following provides the definitions of the aforementioned groups:

- Enrolled subjects are all subjects who sign informed consent.
- 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 that fail screening, are rescreened and are enrolled will be counted both here and with the applicable outcome of their successful enrollment. Those that screen fail twice will only be counted once here.
- 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? (from baseline to week 52)" 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? (from baseline to week 52)" 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 whole study? (Screening through Follow-up)" on the *Study Completion Status* CRF page.
- Safety Population includes any treated subject.

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

Additionally, time to study drug discontinuation for any reason, time to study drug discontinuation due to adverse event, and time to death for any reason will be displayed separately with Kaplan-Meier plots. In the case that subjects are discontinued from treatment administratively to halt the study in preparation for a marketing application, these subjects will be treated as completer/censored for the purposes of these displays. For time to study drug discontinuation, subjects will be censored at the time they complete study treatment. For time to study drug discontinuation due to adverse event, subjects will be censored at the time they complete study treatment or discontinue for another reason.   For time to death for any reason, subjects will be censored at the time they complete study treatment or discontinue for a reason other than death.

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 were collected during the Screening Visit for CR845-CLIN3101 and will reflect what was reported at that time (age, for example, will be age at the CR845-CLIN3101 screening, not the age at the time of participation in the initial study).

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 by treatment group 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)

6.2   Baseline Characteristics

Baseline characteristics of the disease will also be summarized by treatment group 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
- Years on chronic hemodialysis
- Etiology of chronic kidney disease
- Average Baseline Worst Itching Intensity NRS (de novo subjects only)
- Maximum Baseline Worst Itching Intensity NRS (de novo subjects only)

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 ESRD will be calculated as:

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

Years since chronic kidney disease will be calculated as:

(Date of the Screening Visit – first date of CKD+ 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.

Baseline Worst Itching Intensity NRS is calculated as the average of all available scores for de novo subjects prior to dosing. NRS scores are collected at Dialysis Visits 1, 2, 3, and 4. Maximum baseline Worst Itching Intensity NRS will be the maximum value of all available scores per subject.

6.3 Medical History

Medical history data consisted of a fixed list of conditions to be checked off and any additional self-reported medical conditions not contained on the list. Both types of medical history will be coded using *Medical Dictionary for Regulatory Activities* (MedDRA) version 20.0; however, the pre-specified medical history will use the fixed list of conditions as preferred terms and map to the most appropriate system organ class (SOC) based on MedDRA and medical review. Medical history terms that were not pre-specified will be coded for SOC and preferred term. Both types of conditions (selected from the fixed list or self-reported) will be combined and summarized by MedDRA SOC, preferred term, and treatment group. Both types of conditions will also be reported together for separate summaries of conditions related to dialysis, and conditions not related to dialysis. 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 within 14 days prior to the start of treatment through the Follow-Up Visit. These will be coded using the June 2017 DDE B2 *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 month 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 by treatment group 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 class/ingredient. 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 (i.e., Follow-Up Visit). Concomitant medications will be summarized by treatment group 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 class/ingredient. 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

Prescribed anti-itch medications are identified as medications where "Yes" is checked on the *Previous or Concomitant Medications* CRF page to the question "Was this medication used to treat pruritus?"

The prior and concomitant medication summaries described in Sections 6.4.1 and 6.4.2 will be repeated for the prescribed 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 52 weeks, for a total of approximately 156 doses of study drug administered immediately following each dialysis session.

The following variables will be summarized by treatment group:

- Duration of treatment (weeks), from first dose to Week 52
- Duration of continuous treatment (weeks), defined as the longest treatment period with no gap in treatment greater than 28 days spanning first dose to Week 52
- Total duration of treatment (weeks), from first dose to Week 52; for this, gaps greater than 28 days will be removed from the exposure
- Duration of study, from first dose to end of participation date (weeks)
- Number of subjects with continuous treatment of at least 12 weeks, 24 weeks, 36 weeks, 48 weeks
- Number of subjects with total duration of treatment of 12 weeks, 24 weeks, 36 weeks, 48 weeks
- Average dose per administration (mcg/kg)
- Total number of doses actually received (1-12, 13-24, 25-36, etc.)
- Number of missed doses
- Total number of dialysis visits logged (1-12, 13-24, 25-36, etc.)
- Number of missed dialysis visits
- Total treatment exposure in subject-years
- Percentage of planned doses
- Percentage of planned dialysis
- Number of subjects with extra doses
- Number of subjects with extra dialysis visits

Duration of treatment (weeks) = **(**(Date of first dialysis after last dose) – (Date of first dose) + 1**)**/7.

Duration of continuous treatment (weeks) = Duration of treatment, if subject has no gap between treatments that exceeds 28 days, divided by 7. A gap length is defined as Dose date(later) – Dose date (earlier) – 1; thus, a subject dosed on Day 1 and Day 28 would have a gap of 26 days. If a subject has 1 or more gaps, the longest of the gap-free periods will be the duration of continuous treatment. This will be calculated as (date of first dialysis after last dose in selected period) – (Date of first dose in selected period) + 1.

Total duration of treatment (weeks) = Duration of treatment, if subject has no gap between treatments that exceeds 28 days, divided by 7. See continuous treatment above for the definition of a gap. For subjects with gaps, the total duration of treatment will be

the sum of all the gap-free spans, with each period duration defined as: (Date of first dialysis after last dose in selected period) – (Date of first dose in selected period) + 1. In cases of single isolated doses, the duration will run to the next dialysis or 3 days, whichever is smaller.

Duration of study (weeks) = **(**(End of participation date, including follow-up) – (Date of first dose) + 1**)**/7.   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.

Percent of Planned doses = 100* (1 – (number of missed doses / (number of actual doses + number of missed doses – number of extra doses))).

Percent of Planned dialysis = 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 52. Anything more will be counted as extra doses; anything less will be counted as missed doses.
3. Subjects who do not complete through Week 52 will be checked for how far they were into the week that they discontinued: 1,2 days means that they should have 1 dose; 3,4 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.   EFFICACY EVALUATION

No efficacy analyses will be performed.

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

All safety analysis will be performed using the Safety Population based on the treatment the subject actually received after randomization in the prior study (or de novo status). All safety endpoints will be summarized by prior study treatment group/de novo status (and visit as appropriate).

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 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 a screen failure.

All tabular adverse event summaries will be for treatment-emergent adverse events (TEAEs). Treatment-emergent adverse events are defined as those events 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.

Given that worsening of a pre-existing condition should be captured as an adverse event if the frequency, intensity, or character of the condition worsens after the use of study drug as judged by the investigator, for purposes of analysis, TEAEs are identified as any adverse event starting 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).

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 20.0. 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 one episode of an adverse event, the subject will be counted once for that preferred term. If a subject had more than one adverse event in a SOC, the subject will be counted only once in that SOC. The summary tables will include incidence of overall SOC as well as for preferred terms within each SOC. Incidence will be presented for SOC by decreasing frequency overall and then alphabetically and by PT 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. For each treatment group, 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. For each treatment group, 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 TEAEs of special interest (AESIs), will be presented by treatment group. 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

Incidence rate will be calculated for AESIs, serious TEAEs, and TEAEs leading to death. Incidence rate for serious TEAEs and TEAEs leading to death will be summarized by SOC and preferred term. Incidence rate for AESIs will be summarized by preferred term

only. Incidence rate will be calculated as (1000 * the number of events)/total person-years, where total person-years is the sum across all subjects in the treatment group of the individual subject risk times, and individual subject risk time is the number of days from first dose to the last day of the period where an event would be deemed to be treatment emergent.

The summary statistics will be presented for the time to first onset among subjects with a given AESI will be presented for each AESI. Additionally, the durations will be summarized with descriptive statistics; if a subject has more than one AE within and AESI category, the longest duration will be summarized. This will also be presented for a subset of common AEs.

To explore the duration and temporal relationship of AESIs, a graphical representation of occurrences and durations of AEs within each AESI will be presented with subjects on the y-axis and time on the x-axis (Swimmer plot). 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 for each treatment group. Incidence of all infections will be summarized by preferred term.

The following summary tables will be presented for the Safety Population, by treatment group and overall:

- An overall summary showing the number and percentage of subjects with TEAE, serious TEAE, related TEAE, severe TEAE, related serious TEAE, TEAE leading to dose interruption, TEAE leading to study drug discontinuation, TEAE leading to study discontinuation, and TEAE of special interest. This table will also include number of events.
- 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
- Incidence of most common TEAEs (2% or more of subjects across all treatment groups) by preferred term
- Incidence of TE AESIs by preferred term
- Incidence of TE AESIs by preferred term reported by 12-week periods
- Prevalence of TE AESIs by preferred term reported by 12-week periods
- Incidence rate of TE AESI by preferred term
- Incidence rate of serious TEAE by SOC and preferred term
- Incidence rate of TEAEs leading to death by SOC and preferred term
- Incidence of TEAES categorized based on Custom MedDRA query (CMQ)

- Incidence of infections by preferred term

- Incidence of infections potentially related to uremic pruritis by preferred term

Treatment-emergent adverse events of special interest will be reported both in the TEAE displays and separately by preferred term. The prevalence and incidence of AESIs (by special interest term) will be displayed graphically in 12-week intervals.

Additionally, to calculate the incidence of AESIs by 12-week periods, events will be categorized as those with the start date falling from Day 1 (day of first treatment) to Day 84; Day 85 to Day 168; Day 169 to Day 252; and Day 253 to Day 336. Four displays will be generated: subjects with at least 12 weeks of risk; subjects with at least 24 weeks of risk; subjects with at least 36 weeks of risk; and subjects with at least 48 weeks of risk. Time at risk is defined as first dose through the Follow-up Visit or 7 days after last dose , if the Follow-up Visit was not conducted. For example, a subject with last dose on Day 82 and the Follow-up Visit on Day 87 would have 87 days of risk; a subject with last dose on Day 82 and no Follow-up Visit would have 89 days of risk; in both cases, the subjects would be considered to have at least 12 weeks of risk. Subjects that die will have their death day as the end of the time at risk. Within each display, the events will be presented by the 12-week periods detailed above. Denominators will be the number of subjects meeting the time at risk criteria for that display.

Prevalence of AESIs by 12 week period will be calculated in similar manner to the incidence. For the first period, AEs with the start date falling from Day 1 (day of first treatment) to Day 84 will be counted. For subsequent periods, AEs that start or are ongoing at any time during that period will be counted. Denominators will be defined as above based on whether the subject had risk time extending into the period. If a subject has more than one event for a preferred term, they will only be counted once for a period.

In addition, all AEs for each subject will be listed in chronological order including subject identifier, age, race, gender, 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.

The incidence of TEAEs in each CMQ category (see Section 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. 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 after the Follow-Up Visit and up to 30 days thereafter should also be documented on an SAE form if they are deemed by the investigator to be "related" to the study drug. Serious adverse events that occur after the Follow-up Visit and up to 30 days thereafter do not need to be documented on an SAE form if they are deemed by the investigator to be "not related" to study drug. A more detailed definition of SAEs is provided in Protocol Section 6.5.1.1.3. The analysis of SAEs is similar to that of adverse events described in Section 9.2.

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 discontinuation will be listed.

9.4 Clinical Laboratory Evaluation

Blood samples will be collected during screening; on Day 1 before study drug administration; and at Weeks 4, 12, 24, 36, and 52 (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 (e.g., 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. If 2 or more evaluations occur in the same visit window, the evaluation closest to the target visit day will be selected for inclusion in the analysis. If multiple evaluations are equally close to the target visit day, then the latest evaluation will be selected for inclusion in the analysis.

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. Clinically important laboratory values based on pre-specified criteria appropriate for the study population will also be summarized.

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 > 3x ULN and total bilirubin >2x 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× upper limit of normal flagged for alanine aminotransferase and aspartate aminotransferase; 2× upper limit of normal flagged for total bilirubin; and 1.5× upper limit of normal flagged for alkaline phosphatase.

Additionally, clinically significant laboratory findings will be reported for hemoglobin, calcium, serum albumin, and phosphate. Ranges are given below.

Test	Low	High
Hemoglobin (g/dL)	<7	>15
Calcium (mg/dL)	<7	>10.5
Serum albumin (mg/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, systolic and diastolic blood pressure, and mean arterial pressure) will be collected during screening; on Day 1 before study drug administration; at Weeks 4, 12, 24, 36, 52 (End of Treatment/ Early Termination); and at the Follow-up Visit. Additionally, dry body weight will be collected during screening; on Day 1 before study drug administration; at Week 4 and every four weeks thereafter; and End of Treatment/ Early Termination. 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 score and the change from baseline score. If 2 or more evaluations occur in the same visit window, the evaluation closest to the target visit day will be selected for inclusion in the analysis. If multiple evaluations are equally close to the target visit day, then the latest evaluation will be selected for inclusion in the analysis. 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).

A second summary will focus on the individual subject measures with the intent of identifying post-baseline abnormalities defined as clinically notable. Descriptive statistics will be used to summarize the number and percentage of subjects with post-baseline results outside the clinically notable ranges specified below. All vital sign values will be considered when evaluating the criteria.

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 treatment group, subject identifier, and date/time of assessment.

9.5.2   12-Lead ECGs

Standard 12-lead ECGs will be performed in triplicate with the subject in a supine position during screening and at Weeks 12, 24, and 52 (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 by treatment group and overall at each time point and 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 visit. Values for ECG parameters will also be listed by subject.

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

Clinically significant ECG abnormalities at screening will be recorded as medical history. Clinically significant abnormalities or worsening of ECG findings observed after the first dose of study drug should be reported as adverse events.

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 # or adverse event # if deemed a clinically significant abnormality.

10. OTHER ANALYSES

10.1 Hospitalizations, Emergency Department Encounters / Observational Stays

The proportion of subjects who were hospitalized as in-patients and the count and percentage of those subjects admitted through the emergency department, undergoing dialysis, and receiving investigational product during hospitalization will be reported along with summary statistics for duration of stay. This summary will be repeated for emergency department encounters/observational stays; additionally, subjects who have *either* hospitalizations *or* emergency department encounters will be summarized.

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.

10.3 ESA and Iron

All ESA and iron usage will be presented in listings.

A thorough analysis of these outcomes will be performed and described in a separate document.

10.4 Inflammatory Biomarkers

The observed value and the change in inflammatory biomarkers (e.g., interleukin-6, interleukin-8, and granulocyte macrophage-colony stimulating factor) from pre-dose to the end of the Treatment Period will be presented. Univariate and multivariate analyses of the change in inflammatory biomarkers will be described in an analysis plan, separate from this document.

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

Reasons for hospitalization and emergency department visits will not be summarized as described in Section 8.8.1 of the protocol, but will be presented in a listing.

As described in Section 10.2 of this document, ESA and iron usage will be presented in a separate report, and their analyses are not included in this SAP.

Baseline single pool Kt/V (spKt/V) will not be summarized with baseline characteristics of the disease as described in Section 8.6.3 of the protocol as Kt/V values were not collected. Age will not be re-derived using the formula described in Section 8.6.3, but will be used as reported on the CRF.

13. STATISTICAL APPENDIX

Not applicable.

14.   REFERENCES

Not applicable.

15. APPENDICES

15.1   Schedule of Events

Study Procedures	Screening[b]	Day 1	Week 4	Week 12	Week 24	Week 36	End of Treatment / Early Termination	7 - 10 days after End of Treatment / Early Termination
			Treatment Period[a] Up to 52 Weeks					**Follow-Up**
Administrative procedures								
Informed consent	X							
Inclusion/exclusion criteria	X	X[c]						
Safety and other evaluations								
Physical examination	X						X	
Record target dry body weight[d]	X	X	[Record every 4 weeks][d]					
Post-dialysis weight (measured weight)		X	X	X	X	X	X	
Pre-dialysis 12-lead electrocardiogram[e]	X			X	X		X	
Pre-dialysis vital signs[f]	X	X	X	X	X	X	X	X
Hematology, serum chemistry (pre-dialysis)	X	X	X	X	X	X	X	
Serum pregnancy test for women of childbearing potential only	X			X	X	X	X	
Worst Itching Intensity NRS (De novo patients only)[k]	X	X						
Record ESA and IV iron usage			X[g]	X[g]	X[g]	X[g]	X[g]	
Record number of missed dialysis visits and reason(s) + incidence of infection and use of antibiotics, as applicable			[Record on an ongoing basis][h] ⟶					

Study Procedures	Screening[b]	Treatment Period[a] Up to 52 Weeks						Follow-Up
		Day 1	Week 4	Week 12	Week 24	Week 36	End of Treatment / Early Termination	7 - 10 days after End of Treatment / Early Termination
Safety and other evaluations								
IV administration of study drug after dialysis, including record of start and stop time of dialysis		X[i]	[Dose after each dialysis up to Week 52 included][i]					
Inflammatory biomarker samples[j]		X		X	X	X	X	
Adverse event monitoring	X	[Record on an ongoing basis][h] ⟶						
Concomitant medications (including antipruritic medications)	X	[Record on an ongoing basis][h] ⟶						
In-patient hospitalization and/or EDE/OBS	X	[Record on an ongoing basis][h] ⟶						

EDE = emergency department encounter; ESA = erythropoiesis-stimulating agent; IV = intravenous; OBS = observation stay

[a]   Each visit during the Treatment Period will coincide with the patient's normal dialysis treatments. The safety assessment visit may occur on any chosen dialysis day of a scheduled week as long as all assessments are completed during that visit. Patients who miss one of the scheduled study visit weeks (eg, Week 4) may complete this visit at their next dialysis treatment if conducted within 2 weeks of the scheduled visit date. The End of Treatment visit will be the first dialysis visit following the last dose of study drug (i.e. first dialysis on Week 53).

[b]   Screening assessments to be conducted up to 14 days prior to start of the Treatment Period on Day 1. Rescreening will be considered on an individual patient basis and must first be approved by the Sponsor or Medical Monitor (see Section 6.2).

[c]   Prior to dosing on Day 1 of the Treatment Period, the inclusion/exclusion criteria will be confirmed.

[d]   The prescription target dry body weight will be captured from the dialysis prescription and will recorded on Day 1 and at the end of every 4 weeks during the Treatment Period (Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52). The date of prescription will also be recorded.

[e]   Electrocardiogram must be performed prior to start of dialysis.

[f]   Vital signs, including body temperature, heart rate, and blood pressure, will be obtained while the patient is in a sitting or semi-recumbent position prior to start of dialysis.

[g]   Total doses of ESA and IV iron administered will be recorded for the 4-week period ending on Weeks 4, 12, 24, 36, and 52.

[h] Adverse events, concomitant medications, and in-patient hospitalizations and/or EDE/OBS will be recorded during the study starting at the Screening Visit.

[i] Administered after each dialysis as an IV bolus. Details in Section 6.4.5.

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

[k] NRS worksheet will be completed at up to 4 dialysis visits for de novo patients (only) during the week prior to the first dose (Day -7 to Day 1) with training conducted on the first dialysis visit on Day -7. One of 4 scores must be >4 for the patient to be included in the study. These criteria for eligibility should not be communicated to the patients.

15.2 Custom MedDRA Query (CMQ) Categories and Preferred Terms

<u>CMQs</u>

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