# STATISTICAL ANALYSIS PLAN

MC2-25-C1

Final V1.0
18 SEP 2023

**A Parallel-group (2-Arm), Randomized, Double-blind, 12-week Trial to Evaluate the Efficacy and Safety of MC2-25 Cream and MC2-25 Vehicle in Subjects with Chronic Kidney Disease-associated Pruritus (CKD-aP)**

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## List of Abbreviations and Definitions of Terms

| Term | Definition |
|---|---|
| AE | adverse event |
| ATC | anatomical therapeutic chemical |
| BMI | body mass index |
| BSA | body surface area |
| CI | confidence interval |
| CGA | clinician's global assessment |
| CKD-aP | chronic kidney disease-associated pruritus |
| COVID-19 | coronavirus disease of 2019 |
| CI | confidence interval |
| CSR | clinical study report |
| CTA | clinician's targeted assessment |
| DBP | diastolic blood pressure |
| FAS | full analysis set |
| ECGs | electrocardiograms |
| EoT | end of treatment |
| ET | early termination |
| FU | follow up |
| g | gram |
| HR | Heart rate |
| IMP | investigational medicinal product |
| LC-MS/MS | liquid chromatography–tandem mass spectrometry |
| LOCF | last-observation-carried-forward |
| LS | least squares |
| MCMC | markov chain monte carlo |
| MedDRA | medical dictionary for regulatory activities |
| MFAS | modified full analysis set |
| MI | multiple imputation |
| MMRM | mixed model of repeated measures |
| NA | not applicable |
| PPS | per-protocol set |

| Term | Definition |
|---|---|
| PRO | patient reported outcome |
| PT | preferred term |
| Q1 | 1st quartile |
| Q3 | 3rd quartile |
| SAE | serious adverse event |
| SAS | safety analysis set |
| SAS® | statistical analysis software (version 9.4 or higher) |
| SAP | statistical analysis plan |
| SBP | systolic blood pressure |
| SD-NRS | skin dryness numeric rating score |
| SE | standard errors |
| SGIC | subject's global impression of change |
| SI-NRS | sleeploss due to itch numeric rating score |
| SOC | system organ class |
| SS | screened set |
| TEAEs | treatment-emergent adverse events |
| temp | body tempreture |
| TESAEs | treatment-emergent serious adverse events |
| WHO-DD | world health organization drug dictionary |
| WI-NRS | worst itch numeric rating score |

# Statistical Analysis Plan

## 1 Purpose of Statistical Analysis Plan

The purpose of the statistical analysis plan (SAP) is to describe in detail all the data, statistical methods, and summary tables required to implement the statistical analysis of MC2-25-C1 (Section 8.0 in the study protocol version 3.0, dated 30 NOV 2022).

This SAP will be finalized before the database lock for the final analysis. Any changes between the statistical methods provided in the clinical study protocol and this SAP will be explained herein; any changes or deviations from this SAP relative to the analyses performed will be fully documented in the clinical study report (CSR). Minor changes or deviations from the templates for tables, and listings need not be documented in the CSR.

## 2 Study Objectives

The primary objective of this study is to explore the clinical efficacy of MC2-25 cream compared to MC2-25 vehicle in adults with chronic kidney disease-associated pruritus (CKD-aP).

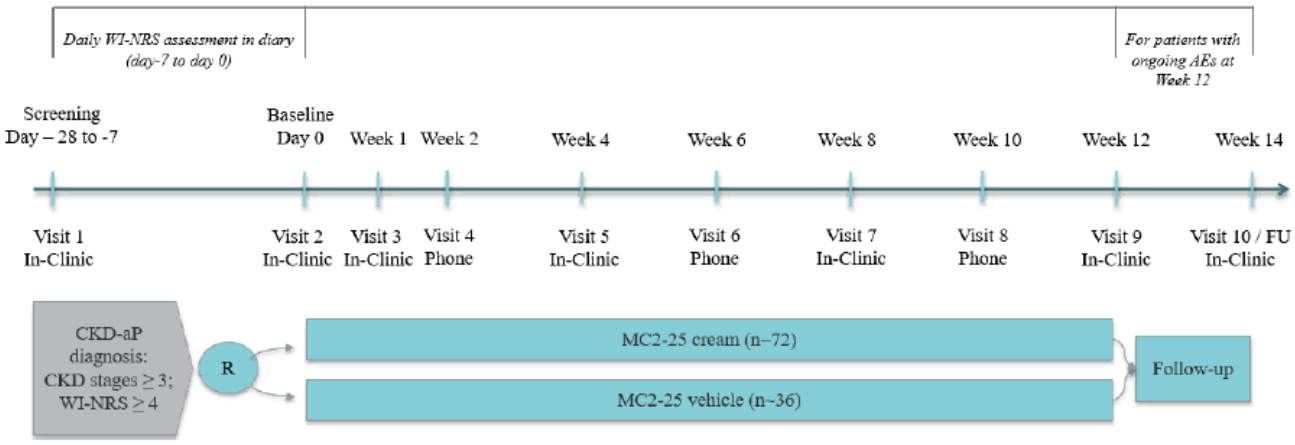
The secondary objective of this study is to explore the safety of MC2-25 cream compared to MC2-25 vehicle in adults with CKD-aP.

Other objective of this study is to explore the subclinical effects of MC2-25 cream in adults with CKD-aP.

## 3 Study Design

This is a multicentre, phase 2, randomized, double-blind, 2-arm, parallel-group, and vehicle-controlled trial in subjects with CKD-aP. Approximately 108 eligible subjects will be randomized in a 2:1 ratio to MC2-25 cream or MC2-25 vehicle, respectively. Subjects will apply the assigned investigational medicinal product (IMP) twice daily for 12 weeks.

**Figure 1 : Study Design**




Subjects will be seen at the trial sites at Screening, Baseline, Week 1, Week 4, Week 8, and Week 12 (end of treatment, EoT). Subjects who have ongoing serious adverse events (SAEs) or related adverse events (AEs) at Week 12 will have a follow-up (FU) visit at Week 14 or (in case

of early treatment discontinuation) 14 days after the EoT visit, whichever comes first. Additionally, phone contacts are planned at Week 2, Week 6, and Week 10.

**Table 1 Schedule of Events**

| **Trial Period** | **Screening Period** | **Treatment Period** | | | | | | | | **FU period[1]** |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number[2]** | **1 (Screening)** | **2 (Baseline)** | **3** | **4** | **5** | **6** | **7** | **8** | **9 (EoT)[3]** | **10 (FU)** |
| **Trial Week** | | **0** | **1** | **2** | **4** | **6** | **8** | **10** | **12** | **14** |
| **Days from Baseline (Visit 2)** *Visit Window* | **-28 to -1** *NA* | **0** *NA* | **7** ***±1*** | **14** ***±2*** | **28** ***±4*** | **42** ***±2*** | **56** ***±4*** | **70** ***±2*** | **84** ***±4*** | ***±2*** |
| In-clinic or Phone Visits[4] | In-Clinic | In-Clinic | In-Clinic | Phone | In-Clinic | Phone | In-Clinic | Phone | In-Clinic | In-Clinic |
| Informed Consent[5] | X | | | | | | | | | |
| Eligibility Assessment | X | X | | | | | | | | |
| Demographics | X | | | | | | | | | |
| CKD History | X | | | | | | | | | |
| Medical History | X | | | | | | | | | |
| CKD-aP Treatment History | X | | | | | | | | | |
| Worst Itch NRS (WI-NRS) – at-home (diary) assessments[6] | | X | X | | X | | X | | X | |
| Worst Itch NRS (WI-NRS) – On-site assessment[7, 8] | X | X | X | | X | | X | | X | |
| Sleeploss due to Itch NRS (SI-NRS)[8] | X | X | X | | X | | X | | X | |
| Skin Dryness NRS (SD-NRS)[8] | X | X | X | | X | | X | | X | |
| Subject's Global Impression of Change (SGIC)[8] | | | X | | X | | X | | X | |
| Subject´s rating of importance of improvement[8] | | | X | | X | | X | | X | |
| Subject's indication of CKD-aP treatment area size[8, 9] | | X | X | | X | | X | | X | |
| 5D-Itch[8] | | X | | | X | | X | | X | |
| Skindex-10[8] | | X | | | X | | X | | X | |
| EQ-5D-5L[8] | | X | | | X | | X | | X | |
| CKD-aP target area identification | | X | | | | | | | | |
| CGA of Skin Appearance | X | X | X | | X | | X | | X | |
| CTA of Skin Appearance | | X | X | | X | | X | | X | |
| Physical examination[10] | X | X | | | | | | | X | (X) |
| Vital signs[11] | X | X | | | X | | X | | X | (X) |
| Single 12-lead ECG | | X | | | X | | | | X | (X) |
| Pregnancy Testing[12] | X | X | | | X | | | | X | (X) |
| Laboratory Assessments[13] | X | X | | | X | | | | X | (X) |

| **Trial Period** | **Screening Period** | **Treatment Period** | | | | | | | | **FU period[1]** |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number[2]** | **1 (Screening)** | **2 (Baseline)** | **3** | **4** | **5** | **6** | **7** | **8** | **9 (EoT)[3]** | **10 (FU)** |
| **Trial Week** | | **0** | **1** | **2** | **4** | **6** | **8** | **10** | **12** | **14** |
| **Days from Baseline (Visit 2)** *Visit Window* | **-28 to -1** *NA* | **0** *NA* | **7** ***±1*** | **14** ***±2*** | **28** ***±4*** | **42** ***±2*** | **56** ***±4*** | **70** ***±2*** | **84** ***±4*** | ***±2*** |
| Imaging of CKD-aP[14] | | X | | | X | | | | X | |
| Randomisation | | X | | | | | | | | |
| Diary (Handout) | X | X | X | | X | | X | | | |
| Biopsy[15] | | X | | | | | | | X | |
| Tape stripping[16] | | X | | | | | | | X | |
| Prior & concomitant therapies[17] | X | X | X | X | X | X | X | X | X | X |
| Adverse events | | X | X | X | X | X | X | X | X | X |
| Investigational medicinal product (IMP) dispensation | | X | | | X | | X | | | |
| IMP return, compliance and accountability | | | | | X | | X | | X | |
| IMP application[18] | | X | | | | | | | | |
| Diary (Review) | | X | X | | X | | X | | X | |

1. Follow-up (FU) visit is only applicable if there are ongoing serious adverse events (SAEs) or related adverse events (AEs) at Week 12. (X) indicates assessments to be performed if judged necessary by the investigator.
2. An unscheduled visit can be conducted to perform any of the postbaseline assessments or procedures included in the SoA if deemed necessary by the Investigator.
3. In the case of trial withdrawal or treatment discontinuation, all assessments of the Week 12 (End of Treatment [EoT]) visit have to be performed. The end of treatment form must be completed when treatment is discontinued and the end of trial form must be completed at end of the trial or in case of trial withdrawal.
4. Phone calls: To remind subjects about diary documentation (in particular once-daily WI-NRS assessments that must be performed for 8 days leading up to each on-site visit [i.e., from day -7 to day 0 where day 0 = next on-site visit day]) and to ask for AEs. Phone visits may be replaced by in-clinic visits where relevant, e.g., in subjects going to the dialysis unit for haemodialysis.
5. Informed consent must be signed by both subject and investigator before any trial-related procedures are performed.
6. At-home (diary) assessments must be performed for 8 days leading up to each visit, i.e., from day -7 to day 0 where day 0 = next on-site visit day.
7. The WI-NRS must also be reported by the subject at on-site visits
8. At all on-site visits, all patient-reported outcome (PRO) assessments should be completed before all other clinical assessments or procedures.
9. The trial staff must estimate the % body surface area treated based on the subject's indication of CKD-aP treatment area size on the CKD-aP treatment area diagram.
10. Physical exam: A complete physical examination is required at Screening and Week 12 (EoT or Early Termination) visits. An abbreviated physical examination is required at the Baseline visit (and if judged necessary by the investigator) at the FU visit if the FU visit is applicable.
11. Vital signs include blood pressure, heart rate, and body temperature measurement. For subjects on haemodialysis vital signs are to be assessed prior to dialysis. Blood pressure and pulse rate will be taken with the subject in the sitting position with approximately 5 minutes rest prior to measurement.
12. Serum pregnancy tests are conducted for women of childbearing potential. At Baseline a urine pregnancy test must also be conducted except for dialysis subjects with anuria.
13. For subjects on dialysis, the blood samples must be collected before dialysis.

14. Only at selected sites and only for subjects who have provided additional consent. CKD-aP target area selected at Baseline. Images of CKD-aP target area must be taken before tape stripping and skin biopsies.
15. Only at selected sites and only for subjects who have provided additional consent. Biopsy: 4 mm skin punch biopsy (optional) is taken from the CKD-aP target area.
16. Tape stripping is conducted in all subjects from the CKD-aP target area.
17. "Therapies" refers to medications and therapies.
18. The first IMP application shall preferably be performed in the clinic under surveillance, and assistance, if necessary, of trial staff.

## 3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the mean change in weekly mean Worst Itch Numeric Rating Score (WI-NRS) recorded in the subject's diary from Baseline to Week 12 for MC2-25 cream compared to MC2-25 vehicle. Weekly mean WI-NRS is calculated as the average of all and at least 4 non-missing WI-NRS values recorded in the subjects' diaries for the 7 days prior to and including the scheduled in clinic visits (8 days in total expected). If less than 4 observations are recorded in the 8 days expected, the weekly mean WI-NRS will be considered missing.

## 3.2 Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint is to compare percentage of subjects obtaining a ≥ 4-point improvement in weekly mean WI-NRS recorded in the subjects' diaries from Baseline to Week 12 between MC2-25 cream and MC2-25 vehicle.

## 3.3 Secondary Efficacy Endpoints

The secondary efficacy endpoints will compare MC2-25 cream and MC2-25 vehicle for following points:

- Percentage of subjects obtaining a ≥ 4-point improvement in weekly mean WI-NRS recorded in the subjects' diaries from Baseline to Week 1, Week 4 and Week 8.
- Percentage of subjects obtaining a ≥ 3-point improvement in weekly mean WI-NRS recorded in the subjects' diaries from Baseline to Week 1, Week 4, Week 8 and Week 12.
- Percentage of subjects obtaining a complete response in weekly WI-NRS recorded in the subjects' diaries from Baseline to Week 1, Week 4, Week 8 and Week 12. Complete response is defined as scores equal to 0 or 1 in ≥ 80% of the non-missing WI-NRS values recorded in the subjects' diaries 7 days prior to and including the scheduled in clinic visits.
- Percentage of subjects obtaining an alternative complete response in weekly WI-NRS recorded in the subjects' diaries from Baseline to Week 1, Week 4, Week 8 and Week 12. Alternative complete response is defined as scores equal to 0 or 1 in ≥ 70% of the non-missing WI-NRS values recorded in the subjects' diaries 7 days prior to and including the scheduled in clinic visits.

## 3.4 Other Efficacy Endpoints

Other endpoints compare MC2-25 cream and MC2-25 vehicle and are:

- Mean change in WI-NRS recorded in the subject's diary from Baseline to Week 1, Week 4, and Week 8.
- Mean change in WI-NRS recorded during on-site visits from Baseline to Week 1, Week 4, Week 8 and Week 12.
- Mean change in Sleeploss due to Itch Numeric Rating Score (SI-NRS) from Baseline to Week 1, Week 4, Week 8 and Week 12.
- Mean change in Skin Dryness Numeric Rating Score (SD-NRS) from Baseline to Week 1, Week 4, Week 8 and Week 12.

**Table 2 WI-NRS, SI-NRS, SD-NRS scale and scores:**

| **Worst Itch/ Worst Sleep Loss/ Worst Skin Dryness in last 24 hours** | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| No Itch/ No Sleeploss/ No Skin Dryness | | | | | | | | | | Worst Imaginable Itch/ Sleeploss/ Skin Dryness |

- Percentage of subjects who reported an improvement in Subject's Global Impression of Change (SGIC) (i.e. "Very much better", "Much better" or "A little better") will be reported for Week 1, Week 4, Week 8 and Week 12 for WI-NRS, SI-NRS and SD-NRS.

Note: SGIC will be summarized for all subjects (see Table 3). Categories 1 to 3 will be summarized as combined "Improvement in SGIC score". Categories 1 to 7 will be summarized individually.

**Table 3 SGIC for itch, sleep loss and skin dryness.**

| **Choose response that best describes overall change in itch, sleep loss and skin dryness since you started taking the trial medication.** | | |
|---|---|---|
| Improvement in SGIC ( 1 to 3) | 1 | Very much better |
| | 2 | Much better |
| | 3 | A little better |
| | 4 | No change |
| | 5 | A little worse |
| | 6 | Much worse |
| | 7 | Very much worse |

- Percentage of subjects who reported "an important improvement" in Subject's rating of importance of improvement (i.e., subjects who respond "Yes" to Question 1 in the 'Subjects rating of importance' assessment) for WI, SI, and SD at Week 1, Week 4, Week 8, and Week 12 or ET.

- Mean change in Subject's indication of CKD-aP treatment area size from Baseline to Week 4, Week 8 and Week 12.

- Mean change in 5D-Itch (Domain Scores and Total Score) from Baseline to Week 4, Week 8 and Week 12

The 5D-Itch consists of 5 domains numbered 1-5.

- Domains 1-3 are single item (question) domains exploring the Duration (Duration domain), Degree (Degree domain) and Direction (Direction domain) of Itch. For each of domains 1-3 the domain score is equal to the value indicated below the response choice (range 1–5).
- Domain 4 (Disability domain) includes four items (questions) assessing the impact of itching on daily activities: sleep, leisure/social activities, housework/errands and

work/school). For domain 4 the score is achieved by taking the highest score on any of the four items (range 1-5).

- Domain 5 (Distribution domain) assesses the number of affected body parts out of 16 possible options. For domain 5 the score is obtained by tallying the number of affected body parts and the sum is sorted into five 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 (range 1-5).
- The total score is achieved by summing together the 5 domain scores and can therefore range between 5 (no pruritus) and 25 (most severe pruritus).
- Continuous descriptive statistics will be provided for all individual domains except Domain 5 from Baseline to Week 4, Week 8 and Week 12.
- Mean change in 5D-Itch Total Score will be presented using continuous descriptive statistics from Baseline to Week 4, Week 8 and Week 12.

**Table 4 5D- Itch Questionnaire**

| **1. Duration** | **During the last 2 weeks, how many hours a day have you been itching?** | | | | |
|---|---|---|---|---|---|
| | Less than 6hrs a day | 6-12hrs/ day | 12-18hrs/ day | 18-23hrs/ day | All day |
| | 1 | 2 | 3 | 4 | 5 |
| **2. Degree** | **Please rate the intensity of your itching over the past 2 weeks** | | | | |
| | Not Present | Mild | Moderate | Severe | Unbearable |
| | 1 | 2 | 3 | 4 | 5 |
| **3. Direction** | **Over the past 2 weeks has your itching got better or worse compared to the previous month?** | | | | |
| | Completely resolved | Much better, but still present | Little bit better, but still present | Unchanged | Getting worse |
| | 1 | 2 | 3 | 4 | 5 |
| **4. Disability** | **Rate the impact of your itching on the following activities over the last 2 weeks** | | | | |
| • Sleep | Never affects sleep | Occasionally delays falling asleep | Frequently delays falling asleep | Delays falling asleep and occasionally wakes me up at night | Delays falling asleep and frequently wakes me up at night |
| | 1 | 2 | 3 | 4 | 5 |
| • Leisure/ social<br>• Housework/ Errands<br>• Work/ Studies | Never affects this activity | Rarely affects this activity | Occasionally affects this activity | Frequently affects this activity | Always affects this activity |
| | 1 | 2 | 3 | 4 | 5 |

| **5. Distribution** | **Mark whether itching has been present in the following parts of your body over the last 2 weeks. If a body part is not listed, choose the one that is closest anatomically** | | |
|---|---|---|---|
| Head/ Scalp | □ | Top of feet/ Toes | □ |
| Face | □ | Soles | □ |
| Chest | □ | Palms | □ |
| Abdomen | □ | Top of hands/ fingers | □ |
| Back | □ | Forearms | □ |
| Buttocks | □ | Upper arms | □ |
| Thighs | □ | Point of contact w/ clothing | □ |
| Lower Legs | □ | Groin | □ |

- Mean change in Skindex-10 (Domain Scores and Total Score) from Baseline to Week 4, Week 8 and Week 12
  - The Skindex-10 consists of 10 questions (beginning with "During the past week, how often have you been bothered by…..") exploring the impact of itch on 3 domains (disease, mood/emotional distress and social functioning) with a 1 week recall period.
  - Each question must be scored on a 7-point scale ranging from 0 (never bothered) to 6 (always bothered).
  - The domain scores are the sums of the following: disease domain (questions 1 to 3), mood/emotional distress domain (questions 4 to 6), and social functioning domain (questions 7 to 10).
  - The total score is the sum of the numeric value of each answered question. The total score ranges from 0 to 60.
  - Continuous descriptive statistics will be presented for individual questions (Q1- Q10).
  - Domains **(1)** Disease (Q1- Q3), Domain **(2)** Mood/ Emotional Distress (Q4 – Q6) and Domain **(3)** Social Functioning (Q-7 – Q10) will be presented using continuous descriptive statistics.
  - Mean change in Total Skindex-10 Score will be summarized descriptively from Baseline to Week 4, Week 8 and Week 12.

**Table 5 Skindex-10 Questionnaire**

| **During the past week, how often have you been bothered by:** | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 0 (Never bothered) | 1 | 2 | 3 | 4 | 5 | 6 (Always bothered) |
| 1. Your itching | □ | □ | □ | □ | □ | □ | □ |
| 2. The persistence/ reoccurrence of your itching | □ | □ | □ | □ | □ | □ | □ |
| 3. The appearance of your skin from scratching | □ | □ | □ | □ | □ | □ | □ |
| 4. Frustration about your itching | □ | □ | □ | □ | □ | □ | □ |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 5. Being annoyed about your itching | □ | □ | □ | □ | □ | □ | □ |
| 6. Feeling depressed about your itching | □ | □ | □ | □ | □ | □ | □ |
| 7. Feeling embarrassed about your itching | □ | □ | □ | □ | □ | □ | □ |
| 8. The effects of your itching in interactions with other | □ | □ | □ | □ | □ | □ | □ |
| 9. The effects of your itch on your desire to be with people | □ | □ | □ | □ | □ | □ | □ |
| 10. The effect of your itching making hard to work or do things you enjoy | □ | □ | □ | □ | □ | □ | □ |

- Mean change in EQ-5D-5L (Visual analogue scale [VAS] and Index value) from Baseline to Week 4, Week 8 and Week 12

  Note: EQ-5D-5L Index Value (calculated using EQ5D5L algorithm) and VAS (i.e., Your Health Today Question) will be analyzed separately.

  **EQ-5D-5L Index Value:**

  The EQ-5D-5L descriptive system comprises five dimensions (5D) (MOBILITY, SELF-CARE, USUAL ACTIVITIES, PAIN / DISCOMFORT and ANXIETY / DEPRESSION), each dimension has five response levels (5L): no problems, slight problems, moderate problems, severe problems, unable to/extreme problems. The respondent is asked to indicate his/her health state by checking the box next to the most appropriate response level for each of the five dimensions.

  A unique health state is defined for each subject by combining the response levels from each of the five dimensions. EQ-5D-5L health states can thus be summarized using the 5-digit code summary number, which reflects how good or bad a health state is according to the preferences of the general population of a country/region.

  To compare two or more health states with each other or to understand which dimension has a greater impact on health-related quality of life (HRQoL), an index value derived from a set of utility values is given to each unique health state. This index value is needed to summarize how good or bad each health state is on a scale anchored at 1 (full health) and 0 (a state equivalent

to dead). Values less than 0 represent health states considered to be or modelled as worse than dead.

The utility values are based on the views and preferences of the general public and numerous country-specific value sets were produced by EuroQol Research Organization for EQ-5D-5L. The EQ-5D-5L index value for this study will be calculated for patients in United Kingdom using English Population Value Set, and for Germany, Hungary and Poland, using German population value set, Hungarian population value set, and Polish population value set respectively as presented in Table 6**.**

An index value thus calculated based upon below mentioned value sets can range anywhere between -1 and 1.

**Table 6 EQ 5D 5L Values sets for United Kingdom (UK), Germany (GR), Hungary (HR) and Poland (PL)**

| **Activity** | **Scale** | **Score** | **UK Value Set** | **GR Value Set** | **HR Value Set** | **PL Value Set** |
|---|---|---|---|---|---|---|
| Mobility | I have no problem in walking | 1 | 0 | 0 | 0 | 0 |
| | I have slight problem in walking | 2 | 0.058 | 0.026 | 0.035 | 0.025 |
| | I have moderate problem in walking | 3 | 0.076 | 0.042 | 0.054 | 0.034 |
| | I have severe problem in walking | 4 | 0.207 | 0.139 | 0.174 | 0.126 |
| | I am un able to walk | 5 | 0.274 | 0.224 | 0.192 | 0.314 |
| | | | | | | |
| Self Care | I have no problem in washing or dressing myself | 1 | 0 | 0 | 0 | 0 |
| | I have slight problem in washing or dressing myself | 2 | 0.050 | 0.050 | 0.045 | 0.031 |
| | I have moderate problem in washing or dressing myself | 3 | 0.080 | 0.056 | 0.044 | 0.047 |
| | I have severe problem in washing or dressing myself | 4 | 0.164 | 0.169 | 0.152 | 0.111 |
| | I am un able to wash or dress myself | 5 | 0.203 | 0.260 | 0.125 | 0.264 |
| | | | | | | |
| Usual Activity | I have no problem in performing usual activities | 1 | 0 | 0 | 0 | 0 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | I have slight problem in performing usual activities | 2 | 0.050 | 0.036 | 0.035 | 0.023 |
| | I have moderate problem in performing usual activities | 3 | 0.063 | 0.049 | 0.050 | 0.040 |
| | I have severe problem in performing usual activities | 4 | 0.162 | 0.129 | 0.132 | 0.097 |
| | I am un able to perform usual activities | 5 | 0.184 | 0.209 | 0.059 | 0.205 |
| | | | | | | |
| Pain/ Discomfort | I have no pain and discomfort | 1 | 0 | 0 | 0 | 0 |
| | I have slight pain and discomfort | 2 | 0.063 | 0.057 | 0.043 | 0.030 |
| | I have moderate pain and discomfort | 3 | 0.084 | 0.109 | 0.030 | 0.050 |
| | I have severe pain and discomfort | 4 | 0.276 | 0.404 | 0.215 | 0.261 |
| | I am extreme pain and discomfort | 5 | 0.335 | 0.612 | 0.123 | 0.575 |
| | | | | | | |
| Anxiety/ Depression | I have no anxiety/ depression | 1 | 0 | 0 | 0 | 0 |
| | I have slight anxiety/ depression | 2 | 0.078 | 0.030 | 0.040 | 0.018 |
| | I have moderate anxiety/ depression | 3 | 0.104 | 0.082 | 0.053 | 0.029 |
| | I have severe anxiety/ depression | 4 | 0.285 | 0.244 | 0.168 | 0.108 |
| | I have extreme anxiety/ depression | 5 | 0.289 | 0.356 | 0.079 | 0.232 |
| | | | | | | |

**Overall Utility Value Total (UVT)=** Mobility UVT+ Self Care UVT+ Usual Activity UVT+ Pain/ Discomfort UVT + Anxiety/ Depression (UVT)
**EQ5D5L Index**= 1- Overall UVT (rounded to three decimal points)

**EQ-5D-5L VAS Score**

The VAS records the subject's overall current health on a vertical VAS where the endpoints are labelled "(100) The best health you can imagine" and "(0) The worst health you can imagine." The VAS provides a quantitative measure of the subject's perception of his/her overall health, higher score indicating better quality of life.

**Table 7 EQ-5D-5L VAS**

| | | |
|---|---|---|
| Your Health today | On a rate of 0 to 100 how is your health today, 0 being worst and 100 being best | 0 - 100 |

Mean change in EQ-5D-5L Index score and VAS score will be presented descriptively from Baseline to Week 4, Week 8 and Week 12.

- Percentage of subjects obtaining a ≥ 2-step improvement in Clinician's Global Assessment (CGA) for the following endpoints from Baseline to Week 1, Week 4, Week 8 and Week 12:
  - Skin dryness
  - Skin signs of itch
  - Overall skin appearance(The overall CGA of skin appearance is defined based on the intensity of the individual signs skin dryness and skin signs of itch. In case of difference in intensity of skin dryness and skin signs of itch then the worst intensity shall prevail in the overall CGA of skin appearance)
- Percentage of subjects obtaining a ≥ 2-step improvement in Clinician's Targeted Assessment (CTA) for the following endpoints from Baseline to Week 1, Week 4, Week 8 and Week 12.
  - Skin dryness
  - Skin signs of itch
  - Overall skin appearance (The overall CTA of skin appearance is defined based on the intensity of the individual signs skin dryness and skin signs of itch. In case of difference in intensity of skin dryness and skin signs of itch then the worst intensity shall prevail in the overall CTA of skin appearance)

**Table 8 CGA/ CTA Score**

| CGA/ CTA Score | Skin Dryness Descriptions | Skin Signs of Itch Description |
|---|---|---|
| Clear | No skin dryness | No active signs of itch |
| Almost Clear | Barely perceptible skin dryness | Barely recognizable active skin signs of itch |
| Mild | Easily perceptible skin dryness | Easily recognizable active skin signs of itch |
| Moderate | Moderate skin dryness | Moderate active skin signs of itch |
| Severe | Marked skin dryness | Marked active signs of itch |

- The mean change in weekly mean WI-NRS recorded in the subject's diary will be assessed within both arms (MC2-25 cream and MC2-25 vehicle) for change from Baseline to Week 1, Week 4, Week 8 and Week 12.

### 3.5 Safety Endpoints

- Frequencies of treatment-emergent adverse events (TEAEs), treatment-emergent serious AEs (TESAEs), treatment-related TEAEs (unlikely related, probably related, and possibly related), TEAEs leading to treatment discontinuation or trial withdrawal, and deaths during the trial for MC2-25 cream compared to MC2-25 vehicle.

- Mean change in vital signs (heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and body temperature (temp)) from Baseline to Week 4, Week 8 and Week 12 for MC2-25 cream compared to MC2-25 vehicle.
  Shift in frequencies of clinically significant and not clinically significant vital signs values from Baseline to Week 4, Week 8 and Week 12 for MC2-25 cream compared to MC-25 vehicle.
- Mean change in laboratory assessments (biochemistry and hematology) from Baseline to Week 4 and Week 12 for MC2-25 cream compared to MC2-25 vehicle.
  Shift in frequencies of normal, abnormal and abnormal clinically significant or not clinically significant laboratory values from Baseline to Week 4, Week 8 and Week 12 for MC2-25 cream compared to MC-25 vehicle.
- Shifts in physical examination from Baseline to Week 12 by body area will be displayed.
  Frequencies of normal, abnormal and abnormal clinically significant and abnormal clinically not significant values of physical examination from Baseline to Week 12 for MC2-25 cream compared to MC-25 vehicle.
- Shifts in electrocardiograms (ECGs) from Baseline to Week 4 and Week 12 will be displayed.
  Frequencies of normal, abnormal and abnormal clinically significant and abnormal clinically not significant values from Baseline to Week 4 and Week 12 for MC2-25 cream compared to MC-25 vehicle.
- Percentage of subjects who missed 1 or more dialysis visits during the Double-blind Treatment Period as recorded on end of trial visit. Not applicable (NA) category will be presented for subjects not on dialysis.

### 3.6 Other Endpoints

- Skin stripping results will be provided in a separate report.

## 4 Analysis Populations

The analysis populations are defined as:

- Screened set (SS): all subjects who sign the informed consent form.
- Safety analysis set (SAS): all subjects who are randomized and dispensed trial medication at Randomization/Day 0, excluding subjects to whom trial medication is not dispensed or who return all the trial medication unused. Subjects will be analyzed according to the actual treatment.
- Full analysis set (FAS): all subjects who are randomized. Subjects will be analyzed according to the randomized treatment.
- Modified full analysis set (MFAS): all subjects who are randomized and returned for at least one post-baseline scheduled visit with WI-NRS data. Subjects will be analyzed according to the randomized treatment.
- Per-protocol set: (PPS): a subset of the MFAS subjects who completed the trial with WI-NRS data for Week 12 and are deemed to have no important protocol deviations that could interfere with the objectives of the trial. Important deviations of eligibility criteria and other deviations from the protocol will be assessed. Important deviations from the protocol may lead to exclusion of a subject or data points from the PPS, which could have interfered with the administration of the treatment or the evaluation of the treatment effect. A blind data review meeting will be conducted and decisions on exclusions of any subjects with important protocol deviations leading to exclusions from the per protocol set will be documented before the final trial database is unblinded.

SAS will be used for all safety analyses. FAS, MFAS, and PPS will be used for efficacy analyses.

# 5 Planned Analyses

## 5.1 Methodological Considerations

General Conventions:

- SAS® software (version 9.4 or higher) will be used for all data analyses and tabulations.
- Data for all investigational centers will be pooled for analysis.
- Summary tables will report data based upon the protocol scheduled time points. For patients who are withdrew early from the study, all efficacy assessments captured at the EoT visit will be assigned to the nearest protocol scheduled time point.

Counts and percentages: Categorical variables will be described by summary tables of frequencies (counts and percentages) per treatment group

Descriptive Statistics:
Descriptive summaries of continuous data will include number of non-missing values, mean, standard deviation (SD), median, minimum, maximum and 1st Quartile (Q1) and 3rd Quartile (Q3). Descriptive summaries of categorical variables will include frequencies and percentages. Missing values will not contribute to the denominator of the percentages.

Statistical tests:

Hypothesis Testing- We assume the null hypothesis is that the MC2-25 cream performs less than or equal to the MC2-25 vehicle while comparing change from baseline in WI-NRS score to Week 12.

We assume for alternate hypothesis that there is significant difference between the treatments.

The hypothesis to be tested to address the objective is:

H0: Change from baseline in mean score of weekly mean of WI-NRS to Week 12 for MC2-25 cream ($\delta_0$) <= Change from baseline in mean score of weekly mean of WI-NRS to Week 12 for MC2-25 vehicle ($\delta_1$)

versus

H1: Change from baseline mean score of weekly mean of WI-NRS to Week 12 for MC2-25 cream ($\delta_0$) > Change from baseline in mean score of weekly mean of WI-NRS to Week 12 for MC2-25 vehicle ($\delta_1$)

The primary analysis will be conducted on Mean change in weekly mean WI-NRS Score recorded in the subject's diary from Baseline to Week 12 for MC2-25 cream compared to MC2-25 vehicle and will be analyzed by a mixed model of repeated measures (MMRM).

Statistical tests will be two-sided with $\alpha = 0.05$. Superiority is concluded if a p-value of statistical hypothesis testing is below the level and the estimate of treatment difference is in favorable direction for MC2-25 cream.
Due to the phase 2 type of the trial, no adjustment due to multiple testing will be used.
No interim analyses are planned. SAS® software will be used for all data analyses and tabulations.
Baseline for efficacy and safety summaries is defined as the last observation prior to the first application of IMP except for weekly mean WI-NRS which is the average of at least 4 non-missing WI-NRS values recorded in the subjects' diaries for the 7 days prior to and including the Baseline day. If there are less than 4 observations in the expected 8 days of entries, the baseline will be considered missing for weekly mean WI-NRS.

## 5.2 Handling of Dropouts or Missing Data

### 5.2.1 Missing Data

For the primary and secondary efficacy endpoints, the primary estimands using the FAS, MFAS and PPS will use a treatment policy strategy for missing data. Missing data will be replaced using a multiple imputation (MI) approach. Note, missing data includes dropouts, empty data fields after dropout date will be handled as missing data regardless of reason for drop out. MI will be performed for all populations separately only if there is a difference in populations. Seed numbers for each endpoint will use the randomly generated 4-digit numbers from the table below. Other variables that are included in the imputation model will include treatment, site, country, visit, and key baseline characteristics such as age, gender, race, CKD stage stratum(1) at baseline, and systemic CKD-aP treatment status(2) at baseline. Depending on the pattern of missingness, a 2-step process may be employed. If missing data points occur for an intermediate visit, they will be imputed first using a Markov Chain Monte Carlo (MCMC) method. As a result, a monotone missingness pattern will be obtained for the data to be fully imputed. The subsequent imputation will use general regression for continuous variables and logistic regression for categorical variables under the assumption data are missing at random to produce 20 imputed datasets where the remaining missing data are filled in using 20 separate sets of values. For the categorical secondary variables, the percentages will be calculated from the above imputed data.

(1) CKD stage stratum at baseline= A. ≥40% of subjects must be on dialysis (HD or HDF) and must be CKD stages 4-5 (CKD stage 4-5 dialysis) B. ≥20% of subjects must Not be on dialysis and must be CKD stages 4-5 (CKD stage 4-5 non-dialysis) C. ≥20% of subjects must Not be on dialysis and must be CKD stage 3 (CKD stage 3)
(2) Systemic CKD-aP treatment status at baseline will be flagged as "Yes" if prior/concomitant medication falls within one of the ATC groups provided in Section 6.3.2

**Table 9 Population and Random Seed Number**

| Population | Random Seed Number |
|---|---|
| FAS | 6529 |
| MFAS | 7631 |
| PPS | 9376 |

For each copy of the imputed datasets, both the primary and secondary endpoints involving the same endpoint variable will be analyzed in the same way as described in the primary and secondary analyses in Sections 5.5.1 and 5.5.2, respectively. Results from the copies of the imputed datasets will be synthesized using SAS® Proc MIANALYZE.

Using the FAS for the primary endpoint analyses, a sensitivity analysis will be performed using last observation carried forward (LOCF; treatment policy). If a subject is given prohibited therapy, all missing data and data for visits after the start of prohibited therapy will use the MI approach described above in another analysis (hypothetical strategy).

If deaths occur, further estimands may be defined following a composite endpoint strategy.

There will be no imputation of missing data for the PPS which will use the data as observed following a treatment policy strategy. There will be no imputation of missing data for safety endpoints.

### 5.2.2 Missing Data Handling- A While-on-Treatment Strategy

If, on the week of interest, for both primary and secondary endpoints, data is missing for more than 5 subjects due to permanent premature treatment discontinuation, then imputation will be performed using the missing data imputation approach and by disregarding any available data for those subjects.

### 5.2.3 Analysis Windows

As subjects do not always adhere to the protocol visit schedule, the following rules are applied to assign actual visits to analysis visits. Listed below are the visit windows and the target days for each visit. The reference day is Baseline, Study day 1. If a subject has 2 or more actual visits in 1 visit window, the visit closest to the target day will be used as the protocol visit for that visit window. The other additional visit(s) will not be used in the summaries or analyses, but they can be used for determination of clinically important endpoints. If 2 actual visits are equidistant from the target day within a visit window, the later visit is used.

Table 10 represents the analysis windows assigned for efficacy and safety analysis and the corresponding range of treatment days (window) during which data for a particular nominal visit will be collected. The analysis windows will be calculated from the first application of study product. These are analysis windows that contain, but are not same as, the actual visit windows.

For assessments that are not planned on Week 1, the visit window for such assessments will be starting at Week 4.

**Table 10 Study Period, Visit and Target Day**

| Study Week/ Period | Study Visit | Target Day | Window |
|---|---|---|---|
| Screening | Visit 1 (V1) | -28 to -1 | |
| Baseline/ Week 0 (on site) | Visit 2 (V2) | 1 | 1 |
| Week 1 (on site) | Visit 3 (V3) | 8 (±1) | 2-19 |
| Week 4 (on site) | Visit 5 (V5) | 29 (±4) | 20-43 |
| Week 8 (on site) | Visit 7 (V7) | 57 (±4) | 44-71 |
| Week 12 (on site/EoT) | Visit 9 (V9) | 85 (±4) | 72-92 |
| Week 14 (FU) | Visit 10 (V10) | ±2 Weeks after EoT | |

For the hypothetical strategy, subjects given prohibited therapies will have WI-NRS data set to missing for visits after the start of the prohibited therapies and then missing data will be estimated using MIs. Subjects with an ET visit will be excluded from the PPS analyses. Safety data collected during an ET visit will remain at the Week 12/EoT visit.

Note: As per the CDISC, baseline is defined as Day 1 and not as Day 0. Therefore, there is a difference of one day between study day as defined in protocol and target day (Table 10).

### 5.2.4 COVID-19 Impacted Visits

Since the primary and secondary efficacy endpoints are derived from the subjects' diaries and summaries of other efficacy endpoints and safety endpoints are as observed, there will be no adjustments made for coronavirus disease of 2019 (COVID-19) impacted visits.

## 5.3 Demographics and Background Characteristics

Subject demographics and background characteristics will be summarized for the FAS, MFAS (if it differs from the FAS) and SAS using descriptive statistics by treatment group and overall. Demographics will include age, age-group (<=65, 66–79, and 80 and above years) sex, race,

ethnicity, weight, height, body mass index (BMI). BMI is derived using: BMI ($kg/m^2$) = weight (kg) / [height (m)]$^2$. Background characteristics include CKD stage and duration, whether subjects are on dialysis or not and time in months (month will be calculated as number of days divided by 30) since initiation of dialysis. Number of times subject has dialysis in a week and use of anti-CKD-ap medication (see Section 6.3.2) at baseline will also be reported. Baseline weekly mean WI-NRS, time in months since start of CKD-aP, selected laboratory parameters (Serum Urea, Serum Creatinine) and, baseline CGA and CTA.

Medical and surgical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 and will be summarized using descriptive statistics by system organ class (SOC), preferred term (PT) and by treatment group and overall. If a subject has more than one medical or surgical history event in an SOC or PT, the subject will be counted once within the term.

Subject demographics, background characteristics, and medical history will be listed by country, site and subject.

## 5.4 Subject Accountability

Subjects screened, reason for screen failure, subjects randomized, subject disposition, reason for withdrawal from trial, reason for discontinuation of treatment, and analysis populations will be summarized using descriptive statistics for the SS by treatment group and overall. Subjects screened, subject disposition and populations status will be summarized using descriptive statistics for the SS by site and by treatment group and overall. Major protocol deviations will be summarized using descriptive statistics using the SAS for all sites and by site and by treatment group and overall. Screen failures, subject disposition including reason for discontinuation, and protocol deviations will be listed by country, site and subject.

## 5.5 Efficacy Analyses

All efficacy summaries and analyses will be provided for the FAS, MFAS and PPS (if MFAS and PPS are different than FAS)

### 5.5.1 Primary Efficacy Analyses

The primary endpoint will be analyzed using a mixed model of repeated measures (MMRM) with baseline weekly mean WI-NRS as a covariate and treatment, CKD stage stratum at baseline, systemic CKP-aP treatment status at baseline and visit as fixed factors and subject as a random factor with a 2-sided $\alpha = 0.05$. An unstructured variance/covariance structure will be used. Least squares (LS) means and standard errors (SE) for each treatment group will be displayed along with the difference in LS means between active and vehicle with the corresponding SE, 95% confidence interval (CI) and p-value.

Descriptive summaries and listings by subject and visit will be provided.

#### 5.5.1.1 Subgroup Analysis

Supportive subgroup analyses will be conducted following same model as primary efficacy analyses also in addition to by CKD stage strata and by country on the FAS.
Subject's dialysis information will be listed by subject, country, and site.

### 5.5.2 Secondary Efficacy Analyses

The key secondary and other secondary endpoints will be analyzed using a generalized estimating equations model with baseline weekly mean WI-NRS as a covariate and treatment,

CKD stage stratum at baseline, systemic CKP-aP treatment status at baseline and visit as fixed factors and subject as a random factor with a 2-sided $\alpha = 0.05$. An exchangeable covariance structure will be used. Estimates and SE for each treatment group will be displayed along with the difference in estimates between active and vehicle with the corresponding SE, 95% CI and p-value.

Descriptive summaries and listings by subject and visit will be provided.

### 5.5.3 Other Efficacy Analyses

Descriptive summaries will be provided for all other efficacy endpoints by visit and treatment group. They will also be listed by subject and visit.

The mean change in weekly mean WI-NRS from baseline to Week 1, 4, and 8, respectively, will be analyzed like described for the primary efficacy analysis in Section 5.5.1.

The mean change in weekly mean WI-NRS will be assessed within treatment for both arms (MC2-25 cream and MC2-25 vehicle) for change from baseline for all visits i.e., Week 1, 4, 8 and 12 using a paired T-test.

## 5.6 Other Safety Variables and Analyses

Safety endpoints will be summarized using the SAS by treatment group and overall and will use descriptive statistics only.

### 5.6.1 Product Compliance

Subjects enrolled in the trial are required to apply the IMP twice daily during the 12 week double-blind treatment period starting on the day of randomization (Baseline) and ending on the Week 12 visit date (End of Treatment). The total number of IMP applications and the number of missed applications during this period is recorded in the Treatment Application Record on a daily basis and entered in the eCRF.

**The applications compliance rate for each subject is defined as:**

**Compliance** = (Actual number of applications in treatment period / Number of expected applications in treatment period) * 100.

Where;

**Actual number of applications in treatment period** = Total number of applications applied during the course of the trial as reported in the eCRF

**Number of expected applications in treatment period** = Total number of days from baseline visit (randomization) till Week 12 (EoT) or early withdrawal X 2 (Twice daily application) – 2

**Duration of treatment period** = Total number of days from baseline visit (randomization) till Week 12 (EoT) or early withdrawal

Compliance will be summarized in following categories; less than 80%, ≥80 to ≤100% and >100% (in cases where subject used the medication more than prescribed times a day) and average compliance in each treatment arm. Accumulated subject listings will also be presented for compliance.

100% compliance means the subject applied IMP twice daily as prescribed for total number of days in the trial and there were no missed applications between first and last application.

Descriptive statistics will be used to summarize product compliance for the SAS. Subject listing for compliance will be presented by 4-week periods (Baseline to < Week 4, ≥ Week 4 to < Week 8, and ≥ Week 8 and for overall trial period.

### 5.6.2 Drug Accountability and Extent of Exposure:

As a part of drug/product accountability, the amount of trial product dispensed and returned (used and unused) will be kept during the trial at each visit and at completion of the trial. Each dispensed kit consists of 5 tubes with each tube having a weight of 74.8 grams (tube with cream and label).

Subjects will return all used and unused tubes at Week 4, 8 and 12 visits and all returned tubes which have broken seals will be weighed to determine the residual amount of the IMP. The following averages will be calculated for all subjects as well as for subjects returning at least 80% of the IMP dispensed during the trial:

1. Weight of IMP used during the trial per subject
2. Weight of IMP used during the trial per subject per number of weeks on treatment
3. Weight of IMP used during the trial per subject per % BSA at Baseline
4. Weight of IMP used during the trial per subject per number of weeks on treatment per % BSA at Baseline

Weight of IMP used during the trial per subject = (74.8 grams times the total number of tubes returned at Week 4, Week 8, and Week 12 visits) + (50 grams times the total number of dispensed tubes not returned) – (the sum of the weight of all tubes returned at Week 4, Week 8, and Week 12 visits). Notes: The minimum weight of IMP used is 0 grams. Number of weeks on treatment is defined as the period from first to last application expressed in weeks.

Drug accountability information will be summarized for SAS and listed by subject.

### 5.6.3 Prior and Concomitant Therapies/ Medications

Prior Therapies/ Medications:

Prior Therapies/Medications include any therapy or medication with start date prior to the start of IMP application. They will be classified according to the World Health Organization Drug Dictionary (WHO-DD; version March 2022 Q) as prior medication.

Concomitant Therapies/ Medications:

Concomitant therapies/ medication will include therapies/ medications starting before or after the start of IMP application and continuing after the start of IMP application. They will be classified according to the WHO-DD; version March 2022 Q.

Descriptive summaries will be by WHO-DD Anatomical Therapeutic Chemical (ATC) level 2 and ATC level 4. There will be separate summaries for all prior therapies/ medications, prior therapies/ medications that were ongoing at baseline, and concomitant therapies/ medications.

Prior and concomitant therapies/ medications will be listed by subject.

### 5.6.4 Adverse Events

Adverse events (AE) will be coded using MedDRA version 24.1 terminology. Treatment-emergent adverse events (TEAEs) related TEAEs (unlikely related, possibly related, and probably related), non-serious TEAEs, serious TEAEs (TESAEs), related TESAEs, TEAEs

leading to treatment discontinuation or trial withdrawal, and deaths will be summarized for the overall incidence of at least one event, incidence by SOC and incidence by SOC and PT.

By definition, TEAE is an AE that began after the start of trial medication treatment. TESAE's are any TEAE's that are reported as serious in the eCRF.
Each subject will contribute only once to each of the incidence rates, regardless of the number of occurrences (events) the subject experiences. The number of occurrences for each SOC and PT will also be displayed.

TEAEs will also be descriptively summarized by severity (mild, moderate or severe) and by relationship to IMP [not related or related (unlikely related, possibly related and probably related)]. In summaries of severity and relationship, subjects who report more than one event mapped to the same SOC or PT will be counted only once under the strongest severity and relationship, accordingly.

An AE is treatment-emergent if its date of onset in on or after the first application date of IMP. An AE is related if relationship to IMP is assessed as unlikely related, probably related, or possibly related.

TEAEs, TESAEs, TEAEs leading to treatment discontinuation or study withdrawal and deaths will be listed by subject.

### 5.6.5 Other Safety Endpoints

Other safety endpoints include hematology and biochemistry laboratory values, vital signs, physical examination and ECG findings.

Physical examination and ECG findings will be summarized as categorical variables (Normal, Abnormal not clinically significant, Abnormal clinically significant) by visit.

Hematology and biochemistry laboratory values and vital signs (heart rate, systolic blood pressure, diastolic blood pressure, temperature, height and weight) will be summarized as continuous variables by visit.

The percentage of subjects who missed 1 or more dialysis visits during the Double-blind Treatment Period will also be summarized.

Each of the above parameters will be listed by subject and, if applicable, visit.

## 6 Appendices

### 6.1 Handling of Missing or Incomplete Dates for Adverse Events , Prior and Concomitant Medications

**Adverse Events**

Handling of partial dates is only considered for the start date. An adverse event with a partial start date is considered treatment emergent if:

- only the day is missing and the start month/year is the same or after the month/year of the first application
- the day and month are missing and the start year is the same or greater than the year of the first application date
- the start date is completely missing

**Prior and Concomitant Therapies**

A medication or therapy is considered prior medication or therapy if:

- only the day is missing and the start month/year is prior to the month/year of the treatment start date.
- the day and month are missing and the start year is the same or before than the year of the first dose date
- the start date is completely missing or the medication is not-ongoing.

A medication or therapy is considered concomitant medication if:

- only the day is missing and the stop month/year is the same or after the month/year of the first dose
- the day and month are missing and the stop year is the same or greater than the year of the first dose date
- the stop date is completely missing or the medication is ongoing.

A medication is considered both prior and concomitant if the start date is before the treatment start date and the stop date is after treatment start date or if the medication is ongoing.

## 6.2 Changes in analyses from protocol:

| Section | Detail |
|---|---|
| 3.3 | Percentage of subjects obtaining a complete response in weekly WI-NRS recorded in the subjects' diaries from Baseline to Week 1, Week 4, Week 8 and Week 12.<br><br>As per protocol version 2.0 dated 24 Aug 2022, complete response is defined as scored equal to 0 or 1 in >80% of the non-missing WI-NRS values recorded in subjects diaries 7 days prior to and including the scheduled in clinic visits. Additional tables using the threshold value of 70% will be developed. This is justified by published paper as given below:<br><br>CR845-310302: A Study to Evaluate the Safety and Efficacy of Difelikefalin in Advanced Chronic Kidney Disease Patients With Moderate-to-Severe Pruritus and Not on Dialysis<br><br>Efficacy Assessment Phase (Treatment Period 1): Proportion of subjects who are "complete itch responders" defined as subjects with ⩾ 70% of the non-missing 24-hour WI-NRS scores equal to 0 or 1 at Week 12 of Treatment Period 1. [ Time Frame: Week 12 of Treatment Period 1 ]<br><br>Intensity of itch will be measured using an NRS used to indicate the intensity of the worst itching over the past 24 hours using a 0 to 10 numeric rating scale, where "0" represents "no itching" and "10" represents "worst itching imaginable".<br><br>https://clinicaltrials.gov/ct2/show/NCT05356403?term=cr845&draw=3&rank=20 |
| 3.6 | Deleted analysis as described in Section 4.2 Protocol, Other endpoints<br>-Changes in biomarkers in skin punch biopsy samples from Baseline to Week 12 for MC2-25 cream compared to MC2-25 vehicle. |

## 6.3 Reference Materials

### 6.3.1 EQ-5D-5L Index Value

The EQ-5D-5L descriptive system comprises five dimensions (5D). The respondent is asked to indicate his/her health state by checking the box next to the most appropriate response level for each of the five dimensions.

A unique health state is defined for each subject by combining one level from each of the five dimensions. A total of 3125 possible unique health states is defined in this way. Each state is referred to by a 5-digit code.

For example, working clockwise from the top of the diagram, state 12345 indicates no problems with mobility, slight problems with washing or dressing, moderate problems with doing usual activities, severe pain or discomfort and extreme anxiety or depression, while state 11111 indicates no problems on any of the five dimensions and 55555 indicates extreme problems at each dimension.


| |
|---|
| EQ-5D-5LUserGuide Basic information on how to use the EQ-5D-5L instrument Version3.0 |
| https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/valuation-standard-value-sets/ |
| Parallel Valuation of the EQ-5D-3L and EQ-5D-5L by Time Trade-Off in Hungary<br>DOI link: https://doi.org/10.1016/j.jval.2020.03.019<br>Published Print: 2020-09 |
| Valuation of EQ-5D-5L Health States in Poland: the First EQ-VT-Based Study in Central and Eastern Europe<br>Crossref DOI link: https://doi.org/10.1007/s40273-019-00811-7<br>Published Print: 2019-09 |
| Value Sets for EQ-5D-5L- A Compendium, Comparative Review & User Guide<br>https://doi.org/10.1007/978-3-030-89289-0 |

| |
|---|
| Valuing health-related quality of life: An EQ-5D-5L value set for England<br>DOI: 10.1002/hec.3564 |
| German Value Set for the EQ-5D-5L<br>https://doi.org/10.1007/s40273-018-0615-8 |

### 6.3.2 Systemic treatment CKD-aP can be identified via ATC code Level 3 or 4:

**R06A** Antihistamines for systemic use
**R06AA** Aminoalkyl ethers
**R06AB** Substituted alkylamines
**R06AC** Substituted ethylene diamines
**R06AD** Phenothiazine derivatives
**R06AE** Piperazine derivatives
**R06AK** Combinations of antihistamines
**R06AX** Other antihistamines for systemic use
**H02A** Corticosteroids for systemic use, plain
**H02B** Corticosteroids for systemic use, combinations
**For some of them only Level 4 could be the most specific:**
**N02BF** Gabapentinoids
**N02BG** Other analgesics and antipyretics