Title: 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)

Short title: ITCHINESS

Protocol Number: MC2-25-C1

Regulatory Agency Identifier Number(s): EUDRACT: 2021-006971-40; EUCT: 2022-500044-38-01; IRAS Project ID: 1004785

Publicly Accessible Database Registration Number: NCT05482698

Paediatric Regulatory Details: This clinical trial is not part of a Paediatric Investigation Plan

Phase: 2

Name of Investigational Product (IMP): MC2-25 cream for topical application (MC2-25 cream)

Name of Sponsor Company: MC2 Therapeutics Ltd, 1A Guildford Business Park, Guildford GU2 8XG, United Kingdom

Scientific Contact at Sponsor: Lars Iversen, MD, DMSc, Tel: + 45 30914970
Email: liv@mc2therapeutics.com

Public Contact at Sponsor: info@mc2therapeutics.com

Number of Sites and Countries: Of 23 initiated sites, 18 sites enrolled and randomised subjects: 10 sites in United Kingdom (UK), 3 sites in Hungary, 4 sites in Poland; 1 site in Germany

Publications: None at the time of the final clinical trial report

Result Analysis Stage: Final analysis

Trial Period: 01JUL2022 to 02FEB2024. There were no global interruptions or restarts and no global substantial modifications.

Rationale: CKD (Chronic Kidney Disease) is a serious disease, and patients are often afflicted by severe pruritus, referred to as CKD-associated pruritus (CKD-aP) or uremic pruritus with a major impact on their quality of life. A number of treatment strategies exist for CKD-aP (e.g., optimization of dialysis parameters, topical emollients and analgesics, antihistamines, GABA analogues (gabapentin and pregabalin), kappa opioid agonists (nalfurafine, diefelikefalin), ultraviolet light B (UV-B) phototherapy) but apart from GABA analogues and kappa opioid receptor agonists the evidence supporting their efficacy is limited. Except for nalfurafine, which is only marketed in Japan, and difelikefalin, which carries a risk of gastrointestinal and nervous system side effects, there are currently no approved and marketed drugs for treatment of CKD-aP. The active ingredient Ala-Gln of MC2-25 cream is intended to act as an isocyanate scavenger which could reduce the adverse effects resulting from carbamylation of skin proteins and amino acids such as pruritus and dry skin in CKD-aP

patients. The trial used a randomized, double-blind, vehicle-controlled design to minimize the potential for bias. By using blinding and randomization and including a group that received vehicle, the trial design controlled for potential influences on the results other than those arising from the pharmacologic action of MC2-25 cream.

Objectives, Endpoints, Estimands, and Statistical Methods:

Objectives	Endpoints
Primary	**Primary Efficacy**
• The primary objective was to explore the clinical efficacy of MC2-25 cream compared to MC2-25 vehicle in adults with chronic kidney disease-associated pruritus (CKD aP)	• 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 WI-NRS values recorded in the subject's diary 7 days prior to and including the visits.)
	Secondary Efficacy
	• Percentage of subjects obtaining a ≥4-point improvement in weekly mean WI-NRS recorded in the subject's diary from Baseline to Week 12 for MC2-25 cream compared to MC2-25 vehicle. • Percentage of subjects obtaining a ≥3-point improvement in weekly mean WI-NRS recorded in the subject's diary from Baseline to Week 12 for MC2-25 cream compared to MC2-25 vehicle. • Percentage of subjects obtaining a complete response in weekly mean WI-NRS recorded in the subject's diary from Baseline to Week 12 for MC2-25 cream compared to MC2-25 vehicle. (Complete response is defined as scores equal to 0 or 1 in ≥80% of the non-missing WI-NRS values recorded in the subject's diary 7 days prior to and including the visits and in addition, complete response was alternatively defined with a threshold of ≥70% of the non-missing WI-NRS values.)
	Other efficacy endpoints
	• Mean change in WI-NRS recorded during on-site visits from Baseline to Week 12 for MC2-25 cream compared to MC2 25 vehicle. • Mean change in Sleeploss due to Itch Numeric Rating Score (SI-NRS) from Baseline to Week 12 for MC2-25 cream compared to MC2-25 vehicle. • Mean change in Skin Dryness Numeric Rating Score (SD NRS) from Baseline to Week 12 for MC2-25 cream compared to MC2-25 vehicle. • Percentage of subjects who reported an important improvement in Subject's Global Impression of Change (SGIC) for Worst Itch (WI), Sleeploss due to Itch (SI), or Skin Dryness (SD) at Week 12 for MC2-25 cream compared to MC2-25 vehicle.

Objectives	Endpoints
	• Percentage of subjects who reported "Much better" or "A little better" in SGIC for WI, SI, or SD from Baseline to Week 12 for MC2-25 cream compared to MC2-25 vehicle. • Change in treatment area size from Baseline to Week 12 for MC2-25 cream compared to MC2-25 vehicle. • Change in 5D-Itch (patient reported outcome: itching score in 5 domains) from Baseline to Week 12 for MC2-25 cream compared to MC2-25 vehicle. • Change in Skindex-10 (patient reported outcome: effects of skin disease on patients' quality of life) from Baseline to Week 12 for MC2 25 cream compared to MC2-25 vehicle. • Change in EQ-5D-5L (patient reported outcome: EuroQoL-Quality of Life Questionnaire in 5 dimensions and 5 levels) from Baseline to Week 12 for MC2-25 cream compared to MC2-25 vehicle. • Percentage of subjects obtaining a ≥2-step improvement in Clinician's Global Assessment (CGA) of skin appearance from Baseline to Week 12 for MC2-25 cream compared to MC2-25 vehicle. • Percentage of subjects obtaining a ≥2-step improvement in one or more individual signs or in the Clinician's Targeted Assessment (CTA) of skin appearance from Baseline to Week 12 for MC2-25 cream compared to MC2-25 vehicle
Secondary	
• The secondary objectives were to explore the safety of MC2-25 cream compared to MC2-25 vehicle in adults with CKD-aP.	• Frequencies of Treatment-Emergent Adverse Events (TEAEs), Serious Adverse Events (SAEs), related TEAEs, Adverse Events (AEs) leading to treatment discontinuation or trial withdrawal, and deaths during the trial for MC2-25 cream compared to MC2-25 vehicle. • Changes in mean safety assessments: vital signs (heart rate, systolic blood pressure, diastolic blood pressure, temperature), and blood samples (biochemistry, haematology) from Baseline to Week 12 for MC2-25 cream compared to MC2-25 vehicle. • Frequency of clinically significant abnormal physical examinations and Electrocardiograms (ECGs) from Baseline to Week 12 for MC2-25 cream compared to MC2-25 vehicle • Percentage of subjects who missed 1 or more dialysis visits during the Double-blind Treatment Period.
• Other objectives were to explore the subclinical effects of MC2-25 cream in adults with CKD-aP	• Changes in biomarkers in skin tape stripping samples from Baseline to Week 12 for MC2-25 cream compared to MC2-25 vehicle.

Statistical Analyses: Efficacy analysis: The primary endpoint of the trial, mean change in weekly mean WI-NRS recorded in the subject's diary from Baseline to Week 12 for MC2-25 cream compared to MC2-25 vehicle, was analysed using a mixed model of repeated measures with Baseline weekly mean WI-NRS as covariate and treatment, CKD stage stratum at Baseline, systemic CKD-aP treatment status at Baseline and visit as fixed factors and subject as a random factor with a two-sided $\alpha = 0.05$. Treatment groups were compared for the superiority of MC2-25 cream over MC2-25 vehicle after 12 weeks of treatment. Due to the Phase 2 type of the trial, no alpha adjustment was carried out for secondary endpoints. Safety Analysis: Safety data were summarised using descriptive statistics (sample size (n), mean, Standard Deviation (SD), median, minimum, and maximum) for continuous variables, and frequency distributions (counts and percentages [%]) for categorical variables.

Methodology: This was a multicentre, phase 2, randomized, double-blind, 2-arm, parallel-group and vehicle-controlled trial in subjects with CKD-aP. Subjects were randomised in a 2:1 ratio to MC2-25 cream or MC2-25 vehicle, respectively. The assigned Investigational Medicinal Product (IMP) was applied by the subjects twice daily for 12 weeks.

Subjects were seen at the trial sites at Screening, Baseline, Week 1, Week 4, Week 8, and Week 12 (End of Treatment, EoT). Subjects who had ongoing Serious Adverse Events (SAEs) or related Adverse Events (AEs) at Week 12 had a follow-up visit at Week 14 or (in case of early treatment discontinuation) 14 days after the EoT visit, whichever came first. Additionally, phone contacts took place at Week 2, Week 6, and Week 10.

Number of Subjects (Planned and Analysed): Approximately 108 subjects were planned to be randomized. 111 subjects were randomized in the trial and were analysed.

Diagnosis and Main Criteria for Inclusion and Exclusion: The trial included males or non-pregnant females at least 18 years of age who had chronic (>3 months) kidney disease (CKD) stages G3-G5 (estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2) and at least moderate CKD-aP, defined as WI-NRS ≥4 (i.e., the average of all and at least 4 non-missing scores reported by the subject in the diary for 7 days prior to and including the Baseline day, 8 days in total). Subjects on dialysis (haemodialysis or haemodiafiltration) and not on dialysis were enrolled.

Trial Treatments, Dose, Mode of Administration, and Batch Number(s):

	MC2-25 cream	**MC2-25 vehicle**
Dose	30 mg/g MC2-25	no active ingredient
Mode of administration	Topical application twice daily. in the morning and evening, to areas with CKD-aP. Treatment of all areas with CKD-aP at Baseline had to be continued also for areas becoming itch-free during trial participation and for new areas of CKD-aP identified after the Baseline visit.	
Batch numbers	CH100 CH101	CH100 CH101A

Duration of Trial Treatment: 12 weeks

Summary of Results and Conclusions:

Subject disposition: A total of 141 subjects were screened of whom 30 were not eligible for the trial. A total of 111 subjects were randomized in the trial. Of these, 98 (88.3%) completed the trial and 13 (11.7%) were withdrawn from the trial early.

Demographic and Other Baseline Characteristics: Approximately half of the subjects were male (52.3%). The mean age of the trial population was 63.7 years (ranging from 25 to 93). Most of the subjects were white (77.5%). The mean CKD duration was 115.19 months (SD=114.651) and the mean CKD-aP duration was 36.03 months (SD=62.938). As per planned stratification for the 3 CKD stages, more than 40% of the subjects in each treatment group were in CKD stage 4-5 on dialysis and more than 20% were enrolled in CKD stage 4-5 not on dialysis. 17% of subjects were enrolled in CKD stage 3. Among the 60 subjects on dialysis, the majority (88.3% of the dialysis subjects) were on haemodialysis. Anti-CKD-aP medication was used by 48 (43,2%) subjects at Baseline which was a topical medication in 11 (9.9%) of the subjects and in most cases a systemic therapy (in 37 [33.3%] of the subjects). The mean size of the CKD-aP treatment area was 49.29% (SD=28.117) of the Body Surface Area (BSA) with a comparable size between the treatment groups (48.02% (SD=27.368) in the MC2-25 cream and 51.80 (SD=29.763) in the MC2-25 vehicle group). Overall, the disease severity measured with WI-NRS, CGA and CTA was similar between treatment groups.

No clinically relevant differences between treatment groups were detected regarding the demographic and baseline disease characteristics.

Compliance and Exposure: Mean treatment duration was 81.1 days (SD=15.24) in MC2-25 cream group and 80.1 days (SD=15.96) in the MC2-25 vehicle group. The mean number of applications accounted for 148.1 (SD=37.98) in the MC2-25 cream group and 145.3 (SD=44.25) in the MC2-25 vehicle group. The percentage of subjects who were less than 80% compliant with the protocol specified IMP treatment was similar between treatment groups (15.1% in the MC2-25 cream and 13.5% in the MC2-25 vehicle group). The average amount of cream used per subject during the trial was 1204.10 g (SD=859.198) in the MC2-25 cream group and 1281.13 g (SD=906.711) in the MC2-25 vehicle group. The mean weight of IMP used during the trial per subject per % BSA at Baseline accounted for 36.21 g (SD=44.8491) in the MC2-25 cream group and 58.17 g (SD=148.4791) in the MC2-25 vehicle group.

Efficacy Results: Overall, treatment of CKD-aP with MC2-25 cream for a period of 12 weeks showed a decrease in disease activity for all clinician-reported and patient-reported outcomes but no significant difference compared to vehicle.

- For the primary endpoint a clear reduction in the Least Square (LS) mean weekly WI-NRS from Baseline to Week 12 was observed with both treatments (-3.544 (Standard Error (SE)=0.332) vs -3.788 (SE=0.431)). The difference in LS means (MC2-25 cream minus MC2-25 vehicle, 0.244 (SE=0.533)) did not reveal significant differences between the two treatments. This result was confirmed by all sensitivity analyses.
    - For all visits a significant change from Baseline in weekly mean WI-NRS was observed within treatment arms with the highest change from Baseline at Week 12 but without significant differences between treatment groups.

  - The supportive analysis of CKD stage subgroups revealed a more pronounced improvement in weekly mean WI-NRS of MC2-25 cream compared to MC2-25 vehicle in the subgroup of subjects with CKD stage 4-5 on dialysis. In the subgroups of subjects with CKD stages 3 and 4-5 not on dialysis a more pronounced improvement was observed with MC2-25 vehicle compared to MC2-25 cream. However, the differences between treatments were not statistically significant.

- For the secondary endpoints of WI-NRS improvement by ≥3 or ≥4 points and complete (alternative) response an improvement was observed but without relevant difference between treatment groups. Complete response was defined as scores equal to 0 or 1 in ≥80% of the non-missing WI-NRS values of the diary entries and alternative complete response was defined with a threshold of ≥70% of the non-missing WI-NRS values.
- A reduction in WI-NRS, SI-NRS and SD-NRS recorded during on-site visits, was seen beginning with Week 1 for both treatments without relevant difference between the treatment groups.
- SGIC indicated an improvement of WI, SI and SD (summary of the categories '1-very much better', '2-much better' and '3- a little better') starting already in Week 1. In both treatment groups the percentage of subjects with a SGIC for WI, SI and SD of 'very much better' increased until Week 12 without relevant difference between the treatments. The improvement was considered as 'important' in the vast majority of subjects in both treatment groups.
- A decrease in mean total 5D-itch score and Skindex-10 and domain scores was seen in both treatment groups indicating an improvement of the itch and indicating an improvement of the disease related quality of life during the treatment. No remarkable differences between treatment groups were seen.
- The mean EQ-5D-5L index value and mean Visual Analogue Scale (VAS) score increased with both treatments from Baseline to Week 12 indicating positive effect on the quality of life and in the overall current health. The improvement was more pronounced at all visits in the vehicle group.
- In both treatment groups an improvement of ≥2-steps in overall CGA and CTA of skin appearance was observed starting in Week 1. The highest percentage of subjects with a ≥2-step improvement was seen at Week 12 in both treatment groups with a slightly higher percentage of subjects in the vehicle group.

Safety Results: Overall, treatment with MC2-25 cream in subjects with CKD-aP for a period of 12 weeks was generally well tolerated and no safety concerns were identified.

Adverse Events (AEs) including deaths and other SAEs:

- In total, 130 TEAEs occurred in 55 patients (50.0%). The incidence of events was similar between the treatment groups (49.3% MC2-25 cream vs. 51.4% MC2-25 vehicle). Most TEAEs were of mild or moderate intensity, severe events were reported for 10 subjects (9.6% MC2-25 cream, 8.1% MC2-25 vehicle).
- Overall, 13 TEAEs considered related to IMP were reported for 10 (9.1%) subjects. The proportion of subjects with related TEAEs was similar between treatment groups

(9.6% MC2-25 cream vs 8.1% MC2-25 vehicle). Most of the related TEAEs were in the SOC 'General disorders and administration site conditions' (8.2% MC2-25 cream and 5.4% MC2 vehicle) with the main PT 'Application site pain' observed in 5.5% of subjects in the MC2-25 cream group. The majority of related TEAEs were of mild intensity, none was assessed as severe.

AEs that led to IMP-discontinuation, deaths and TESAEs:

- One subject in the MC2-25 cream group discontinued IMP and was withdrawn from the trial due to an AE ('Pericarditis') which was assessed as unrelated to IMP. Another 11 subjects had IMP interrupted or discontinued due to AEs but were not withdrawn from the trial due to these AEs. This was observed more frequently in the MC2-25 vehicle group (6.8% subjects MC2-25 cream vs. 16.2% subjects MC2-25 vehicle).
- There were 2 death cases (Preferred Term (PT) 'End stage renal disease', 'Diarrhoea') during the treatment period, one in each treatment group, which were both considered not-related to treatment.
- In total 23 TESAEs were reported for 16 (14.5%) subjects, none was considered to be related to the IMP. The proportion of TESAEs was similar between treatment groups (15.1% MC2-25 cream, 13.5% MC2-25 vehicle).

Other safety assessments:

- There were no clinically relevant findings or differences between treatment groups in biochemistry and haematology parameters.
- There were no clinically relevant findings or differences between treatment groups in vital signs, physical examination, or ECGs.
- Percentage of subjects who missed 1 or more dialysis visits was similar between treatment groups. Overall, only few subjects missed 1 or more dialysis visits.

Pharmacodynamic Results: Tape strips from CKD-aP affected skin areas were obtained throughout the trial. However, due to the lack of differentiation between MC2-25 cream and MC2-25 vehicle on the primary and secondary endpoints the tape strips have not been analysed.

Conclusions: The analyses of the primary efficacy endpoint showed an improvement of CKD-aP with MC2-25 cream, but no significant difference compared to MC2-25 vehicle in the treatment of adult subjects with CKD-aP. The results from all efficacy endpoints were in line with showing a positive treatment effect for the active treatment but without significant difference to MC2-25 vehicle.

MC2-25 cream was generally well tolerated, and no safety concerns were identified during the treatment period of 12 weeks. No clinically relevant differences between treatment groups were observed for laboratory parameters and for vital signs, physical examination, and ECG. The evaluation of AEs did not show any clustering in PT.

In this trial, no significant difference in efficacy or safety of MC2-25 cream compared to MC2-25 vehicle was detected in treating CKD-aP and the safety profile was acceptable.

Limitations:

UK sites recruited a large part of CKD stage 3 patients with help from a dedicated recruitment company. This may have led to some degree of selection bias between UK and other countries, as well as CKD 3 and CKD 4-5 groups.

The small sample size – in particular, for the CKD stage 3 group – may lead to imprecise conclusions on effect in that group.

Declaration:

Hereby the submitting party confirms the accuracy of the submitted information.