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ORIGINAL RESEARCH

Long-Term Efficacy and Tolerability of an Emollient Containing Glycerol and Paraffin for Moderate-to-Severe Uremic Xerosis: A Randomized Phase 3 Study

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ABSTRACT

***Introduction*:** There is an unmet need for effective topical therapies for patients with uremic xerosis and chronic kidney disease-associated pruritus (CKD-aP). The long-term efficacy and tolerability of an emollient containing glycerol 15% and paraffin 10% (V0034CR) was evaluated in a phase 3 study.

***Methods*:** In this randomized, double-blind, two-parallel group, vehicle-controlled study, patients with moderate-to-severe uremic xerosis were randomized to once-daily application of V0034CR or vehicle control for 28 days (period I). This was followed by a treatment-free period of ≤21 days (period II), then all patients received open-label treatment with V0034CR for ≥84 days (period III). Outcomes included treatment response at the end of period I (El Gammal's xerosis severity score), instrumental measures of scaling (D-Squame technique), time to relapse during period II, rate of recurrence during period III, pruritus severity over time, patient acceptability, and adverse events (AEs).

***Results*:** The intent-to-treat population comprised 235 patients randomized to V0034CR ($n=118$) or vehicle control ($n=117$) during period I. Treatment response at the end of period I was achieved by 71 patients (60.2%) in the V0034CR group versus 48 (41.0%) with vehicle control ($p=0.0041$). This coincided with greater reductions in the total surface area of squames ($p=0.001$ vs vehicle control). Xerosis relapsed progressively without treatment in period II; however, remission was durable under maintenance therapy in period III. Improvements in pruritus severity were comparable between V0034CR and vehicle control, suggesting that the antipruritic effect of V0034CR was mainly exerted by its oil-in-water emulsion base. V0034CR had high patient acceptability and was well tolerated; the most common treatment-related AEs were irritation or erythema (2.1%),

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exacerbated pruritus (1.3%), and vesicles at the application site (0.9%).
Conclusion: These data support the use of V0034CR, with its hydrating and occlusive properties, for the long-term management of patients with moderate-to-severe uremic xerosis and CKD-aP.
Trial Registration: ClinicalTrials.gov identifier NCT01084148; EudraCT number 2006-002201-31.

PLAIN LANGUAGE SUMMARY

People on dialysis often experience dry and itchy skin that is hard to treat. This study tested the effectiveness of a new moisturizing cream (called V0034CR) in people with dry skin caused by dialysis (also known as uremic xerosis). In this study, 235 people with moderate or severe uremic xerosis were randomly split into two groups. One group (118 people) was given V0034CR cream, which contains glycerol and paraffin as its "active" ingredients. The other group (117 people) was given a "control" cream, which contains the same ingredients as V0034CR cream but without glycerol and paraffin. Both groups applied their assigned cream to their skin once a day for 4 weeks. If a person's dry skin had improved after 4 weeks, then they could stop using the cream for up to 3 weeks, and then switch to V0034CR cream from week 7 until the end of the study (19 weeks). If a person's dry skin had not improved after 4 weeks, or if their dry skin returned after stopping the cream, then they could start using V0034CR cream early and for the rest of the study. The study found that using V0034CR cream improved the signs and symptoms of dry skin more than the control cream. Most people in the study said that V0034CR cream was effective and easy to use, and no serious side effects were reported. The results of this study suggest that V0034CR cream is an effective treatment for people with dry skin caused by dialysis.

Keywords: Chronic kidney disease-associated pruritus; Emollient; Glycerol; Paraffin; Uremic xerosis

Key Summary Points

Why carry out this study?

Topical moisturizers and emollients are the mainstay of basic therapy for conditions associated with xerosis (dry skin); however, existing products often provide limited benefit to people with uremic xerosis and/or chronic kidney disease-associated pruritus (CKD-aP).

This randomized phase 3 study aimed to evaluate the long-term efficacy and tolerability of V0034CR, an emollient that combines the moisturizing and barrier-repairing properties of glycerol with the anti-irritant and occlusive properties of paraffin.

What was learned from the study?

In patients with moderate-to-severe uremic xerosis, once-daily use of V0034CR was associated with greater improvements in investigator-reported and instrumental measures of xerosis versus control, improved the severity of CKD-aP, demonstrated high patient acceptability, and was well tolerated.

These data suggest that the combination of glycerol and paraffin in V0034CR emollient is an effective long-term treatment option for patients with uremic xerosis and CKD-aP.

INTRODUCTION

Uremic xerosis is one of the most common cutaneous complications of maintenance renal dialysis (MRD) among patients with end-stage renal disease (ESRD). The pathogenic and clinical features of uremic xerosis have been reviewed elsewhere [1]; however, it is a poorly recognized condition for which therapeutic research and management have been largely neglected. Uremic xerosis is a chronic and

widespread disease that is closely associated with chronic kidney disease-associated pruritus (CKD-aP), both of which are burdensome conditions that are detrimental to patient quality of life [2–5].

Topical moisturizers and emollients are the mainstay of basic therapy for conditions associated with xerosis (dry skin) [6, 7]. However, it is a common belief among practitioners that current over-the-counter products provide limited benefit in those with uremic xerosis and/or CKD-aP, highlighting a need for new formulations that counteract the pathogenic features of these conditions. For example, reduced stratum corneum levels of glycerol (an endogenous humectant) have been associated with dry skin in patients with ESRD, and reduced skin hydration has in turn been correlated with the presence of CKD-aP [8–12].

V0034CR (Dexeryl®; Pierre Fabre) is an emollient cream containing glycerol 15% and paraffin 10% in an oil-in-water emulsion. The combination of glycerol and paraffin was hypothesized to be pharmacologically relevant in xerosis, based on the moisturizing and barrier-repairing properties of glycerol, and the anti-irritant and occlusive properties of paraffin [6, 13, 14]. Indeed, the synergistic effects of V0034CR on skin hydration and transepidermal water loss were demonstrated in a study of healthy subjects with non-pathological dry skin [15], while other studies have shown the clinical benefits of V0034CR in patients with cutaneous xerosis [16] and related conditions including atopic dermatitis [17–20], ichthyosis [21, 22], psoriasis [23], senile xerosis [24], and diabetic foot xerosis [25].

Based on the hypothesis that V0034CR might also be effective in uremic xerosis and CKD-aP, a randomized, double-blind, vehicle-controlled study was conducted to evaluate the short-term efficacy and tolerability of V0034CR in patients with moderate-to-severe uremic xerosis [26]. After twice-daily application for 7 days, V0034CR was associated with improvements in xerosis which were maintained over 2 months with ongoing treatment, and which coincided with substantial improvements in CKD-aP severity and patient quality of life [26]. Herein, we report the results of a subsequent phase 3 study, which aimed to evaluate the longer-term efficacy, acceptability, and tolerability of V0034CR in patients with moderate-to-severe uremic xerosis.

METHODS

Study Design

This was a phase 3, randomized, double-blind, two-parallel group, vehicle-controlled study conducted at 14 clinical sites across Europe; a list of study sites and investigators is provided in Supplementary Table S1. The study was conducted in compliance with the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice Guidelines, and applicable local laws. The study protocol was approved in each country by applicable independent ethics committees and competent authorities (Supplementary Table S2), and written informed consent was obtained from all participants. This study is registered with ClinicalTrials.gov (NCT01084148) and the European Union Clinical Trials Register (EudraCT 2006-002201-31).

Study Population

Eligible patients were aged ≥ 18 years, receiving MRD (hemodialysis or peritoneal dialysis) due to ESRD, and had moderate-to-severe uremic xerosis. Xerosis severity was assessed using the modified clinical score described by El Gammal and colleagues (0 = smooth skin; 1 = patches of fine, powdery scales; 2 = diffuse ashy appearance with many fine scales; 3 = moderate scaling with beginning of cracks; and 4 = intense scaling, moderate cracks) [27]. Included patients were those with a xerosis severity score of ≥ 2 on at least one of five test areas (both lower legs, the forearm without arteriovenous shunt, the chest, and dorsum of the neck). Patients with a known allergy to one of the test ingredients, or those with a concomitant condition that might have interfered with the study, were excluded. Patients treated with any moisturizing or emollient preparation within 7 days, an unstable dosage of oral antipruritic agents within 4 weeks,

or phototherapy within 8 weeks prior to study entry were also excluded.

Study Treatments

The test product (V0034CR) contained glycerol 15% and paraffin 10% in an oil-in-water emulsion, the constituents of which have been reported elsewhere [17, 25]. The vehicle control was the oil-in-water emulsion without glycerol and paraffin, and has been shown to exert basic hydrating and occlusive effects [15]. The V0034CR and vehicle control creams were identical in color and appearance, and were packaged in identical tubes.

Study Periods

After screening, eligible and consenting participants entered a washout period free of topical treatments for 7 days for all patients, and with a stable dosage of oral antihistamines for 14 days for those with CKD-aP. Thereafter, the study comprised three periods with varied designs (Fig. 1). At the start of period I, patients were randomized to receive V0034CR or vehicle control, and instructed to apply the allocated product once daily for 28 days (initial treatment period). Patients were advised to apply approximately 1 mg/cm^2 of product to xerotic areas; to improve compliance, patients were provided with a table indicating the number of fingertip units (corresponding to approximately 1 g of product per unit) to apply on each body region. Patients were provided with one 250-mL tube of V0034CR or vehicle control at each weekly study visit during period I (i.e., at baseline and days 7, 14, and 21).

On day 28, patients with no persisting lesions (defined as all test areas with a xerosis severity score < 2) entered a treatment-free period of up to 21 days (period II; Fig. 1). Those with persisting lesions did not undergo a treatment-free period, instead entering period III on day 28. For patients who entered period II, weekly study visits continued and patients were assessed for relapse. Those with relapsing lesions (xerosis severity score ≥ 2 on at least one test area) on day 35 or day 42 entered period III on those days. Patients with no relapsing lesions at either of these visits continued the treatment-free period up to day 49 (Fig. 1). During period III, all patients received open-label V0034CR emollient, which was applied ad libitum by the patients on the basis of their lesional status, tolerance, and acceptability of the product (maintenance treatment period). Study visits were carried out every 4 weeks from day 49 through

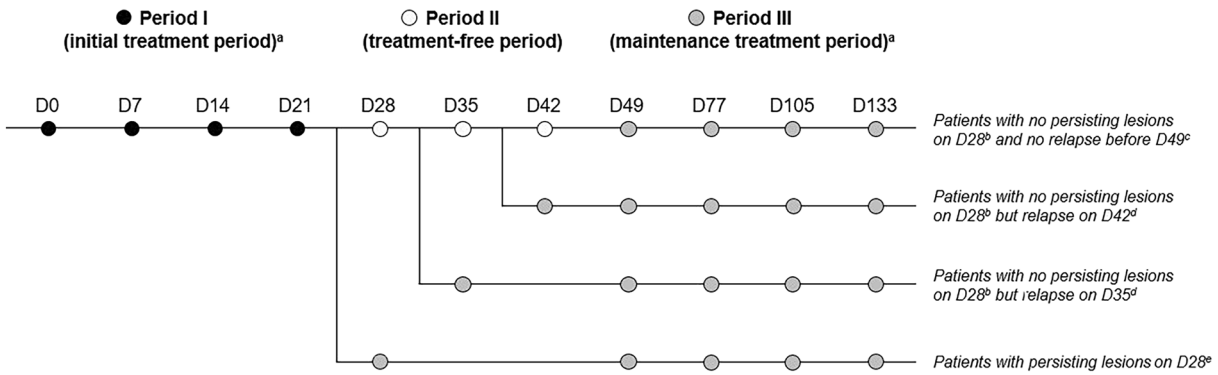

Fig. 1 Study periods and visits according to response to the treatment. Circles indicate study visits for each patient subgroup; shading indicates the study period (black = period I; white = period II; gray = period III). [a]In period I, patients were instructed to apply their assigned treatment (V0034CR or vehicle control) once daily for 28 days (~ 1 mg/cm^2 to xerotic areas); in period III, all patients applied V0034CR ad libitum through day 133. [b]Xerosis severity score < 2 was achieved for all five test areas at the end of period I. [c]Xerosis severity score < 2 was maintained for all five test areas during period II. [d]Xerosis severity score ≥ 2 on at least one test area during period II. [e]Xerosis severity score ≥ 2 on at least one test area at the end of period I. *D* day

day 133, and patients received the equivalent of one 250-mL tube of V0034CR per week at each visit during period III.

Outcomes

The primary efficacy outcome was the rate of treatment response at the end of period I, which was defined as a xerosis severity score < 2 on all test areas and a score reduction from baseline of ≥ 2 on at least one test area. To minimize intra- and interobserver variability, a photograder illustrating each grade was given to each investigator. To accompany investigator-reported xerosis severity, instrumental measures of scaling using the D-Squame technique [28] were performed on one lower leg at baseline and at the end of period I. These secondary outcomes included the total surface area of squames (SURFT) and the mean optical density of squames (MOD). The other primary efficacy outcome was time to relapse during period II, defined as the recurrence of xerosis severity score ≥ 2 on at least one test area in patients with no persisting lesions at the end of period I.

Other secondary outcomes included the time course of the total xerosis severity score (sum of scores for all five test areas); the rate of recurrence during period III (defined as a xerosis severity score of ≥ 2 on at least one test area in patients with remitting lesions at day 49); the global severity of pruritus over time, as assessed by the patients using 100-mm visual analog scales (VAS) at each study visit; change from baseline in quality of life (QoL) assessed using the Short Form-12 (SF-12) [29] and the Dermatology Life Quality Index (DLQI) [30], at the end of periods I and II; and the acceptability of V0034CR based on efficacy, ease of use and local tolerance, as assessed by the patients using 4-point scales (very satisfactory to not satisfactory at all, or very good to very poor) at study end. Adverse events (AEs) and patient compliance (i.e., frequency of product application and weight of returned product tubes) were also assessed throughout the study.

Statistical Analysis

Efficacy and safety analyses were performed on the intent-to-treat (ITT) population, defined as all randomized patients who received at least one application of V0034CR or vehicle control. Missing data during period I were replaced using last observation carried forward methodology; missing data during period II were imputed using last observation carried backward. The rate of treatment response during period I was assessed using Fisher's exact test, and time to relapse during period II was evaluated by the log-rank test. Secondary outcomes were analyzed using Wilcoxon signed-rank tests; Student's *t* tests could be used to analyze SURFT and MOD if the data were distributed normally (determined using the Shapiro–Wilk test). Descriptive analyses were performed for product acceptability, local tolerance, and AEs. A significance level of 5% was applied to all statistical tests, which were performed using SAS version 8.2 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Study Population

In total, 236 patients with moderate-to-severe uremic xerosis were enrolled and randomized to receive V0034CR ($n = 118$) or vehicle control ($n = 118$). One patient randomized to the vehicle control group withdrew their consent before applying any product, and thus was excluded from the ITT population. Accordingly, the ITT population comprised 235 patients in period I ($n = 118$ in the V0034CR group and $n = 117$ in the vehicle control group), 144 patients in period II ($n = 83$ and $n = 61$, respectively) and 205 patients in period III ($n = 97$ and $n = 108$, respectively; Fig. 2). No patients were lost to follow-up during the study.

Baseline demographics and lesional status of the study population are summarized in Table 1. Most baseline characteristics were comparable between treatment groups, except for CKD-aP, which had a longer duration in the V0034CR group versus vehicle control ($p = 0.0425$).

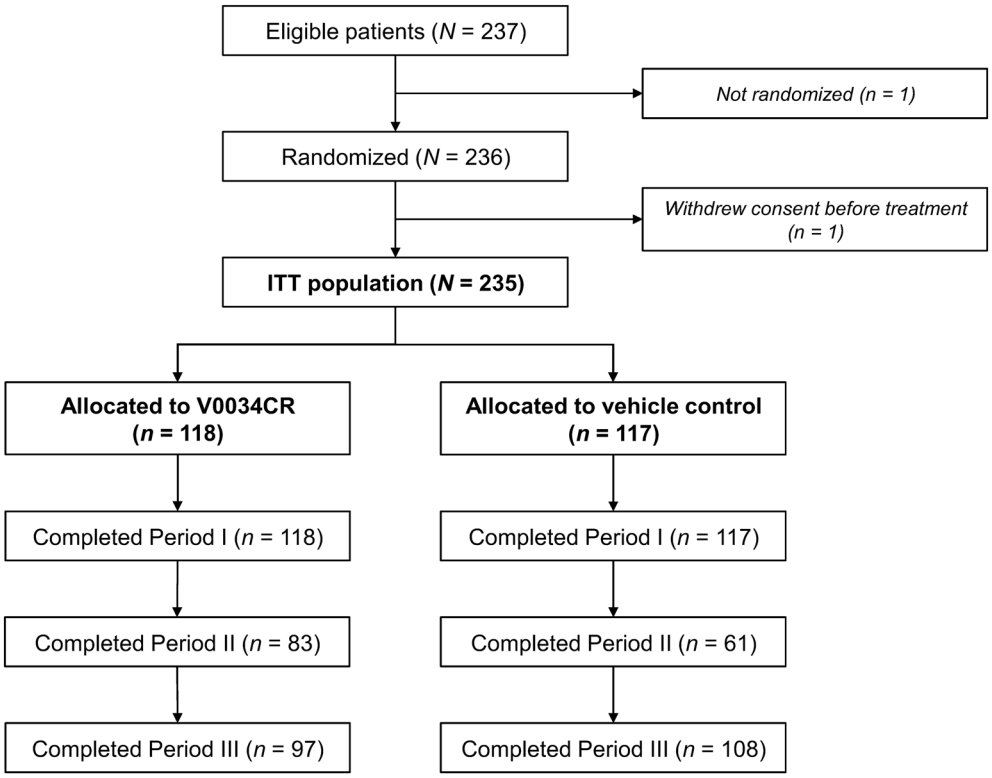

Fig. 2 Patient disposition flowchart. *ITT* intent-to-treat

Long-Term Efficacy of V0034CR

Treatment response at the end of period I was observed in 71 patients (60.2%) in the V0034CR group and 48 patients (41.0%) in the vehicle control group (Fig. 3a). The difference in treatment response in favor of V0034CR was statistically significant ($p=0.0041$). Instrumental measures of scaling by D-Squame confirmed the investigator assessments of xerosis severity (Fig. 3b). At the end of period I, there was a significant difference in favor of V003CR over vehicle control for SURFT (mean ± standard error [SEM], 5997.2 ± 1484.4 vs 8783.5 ± 1558.5 mm^2, respectively; $p=0.001$), and a trend in favor of V0034CR for MOD (4.3 ± 0.5 vs 4.9 ± 0.5; $p=0.0865$).

Time to relapse during period II (among those with no persisting lesions at the end of period I) is shown in Table 2. Despite a trend for longer time to relapse in the V0034CR group, no significant difference between treatment groups was found.

The time course of the total xerosis severity score during the study is illustrated in Fig. 4a. Total xerosis severity scores in the V0034CR group were rapidly reduced after treatment initiation (i.e., as early as day 7), and were significantly lower than that of the vehicle control group at the end of period I (mean ± SEM, 3.1 ± 0.3 vs 4.3 ± 0.3; $p=0.002$). The benefit of V0034CR treatment was partially maintained during period II and up to the start of period III (4.3 ± 0.3 vs 5.4 ± 0.2; $p=0.003$). Maintenance therapy during period III further contributed to the normalization of total xerosis severity scores in the V0034CR group (1.7 ± 0.2 on day 133), whereas patients originally randomized to the vehicle control achieved clinical regression of xerosis after 1 month of V0034CR maintenance therapy (2.4 ± 0.3 on day 77) and through to study end (1.9 ± 0.3 on day 133). No

Table 1 Baseline patient demographics and clinical characteristics (intent-to-treat population)

	V0034CR (*n* = 118)	**Vehicle control (*n* = 117)**
Age (years), mean ± SEM	64.8 ± 1.3	64.5 ± 1.2
Male sex, *n* (%)	70 (59.3)	64 (54.7)
Underlying renal disease, *n* (%)		
Glomerular diseases	41 (34.7)	24 (20.5)
Diabetic nephropathy	28 (23.7)	25 (21.2)
Nephrosclerosis	24 (20.3)	32 (27.1)
Polycystic kidney	6 (5.0)	10 (8.4)
Congenital nephropathies	0	1 (0.8)
Pyelonephritis	7 (5.9)	13 (11.0)
Others	25 (21.2)	17 (14.4)
Unknown	1 (0.8)	4 (3.4)
Type of MRD, *n* (%)		
Hemodialysis	117 (99.1)	114 (97.4)
Peritoneal dialysis	1 (0.9)	3 (2.6)
Duration of MRD (years), mean ± SEM	4.9 ± 0.4	4.4 ± 0.4
Duration of xerosis (years), mean ± SEM	4.5 ± 0.4	4.1 ± 0.4
Severity of xerosis (total score), mean ± SEM	8.2 ± 0.3	8.4 ± 0.3
Patients with CKD-aP, *n* (%)	75 (63.6)	72 (61.5)
Duration of CKD-aP (years), mean ± SEM[a]	4.4 ± 0.5	3.5 ± 0.5
Severity of CKD-aP (100-mm VAS), mean ± SEM	36.2 ± 3.0	35.7 ± 3.3

CKD-aP chronic kidney disease-associated pruritus, *MRD* maintenance renal dialysis, *SEM* standard error of the mean, *VAS* visual analog scale

[a]Significant difference between groups, based on Wilcoxon signed-rank test ($p = 0.0425$)

significant differences in total xerosis severity scores were observed between the two groups from day 77 through to study end. Among patients in both groups with remitting lesions at day 49 ($n = 140$), the incidence of recurrence during period III was low (2.1% on day 133).

Patient-Reported Outcomes

In parallel with reductions in investigator-assessed xerosis severity, an early and marked relief of CKD-aP was reported by patients in the V0034CR group; however, changes in pruritus severity over time were not significantly different to that reported in the vehicle control group ($p > 0.05$ at all time points; Fig. 4b). Mean ± SEM pruritus VAS scores were comparable between the V0034CR and vehicle control groups at the end of period I (16.9 ± 2.2 vs 15.1 ± 2.0 mm, respectively); after a slight rebound during period II and up to the start of period III (20.2 ± 2.7 vs 19.3 ± 2.5 mm), pruritus was further decreased in both groups

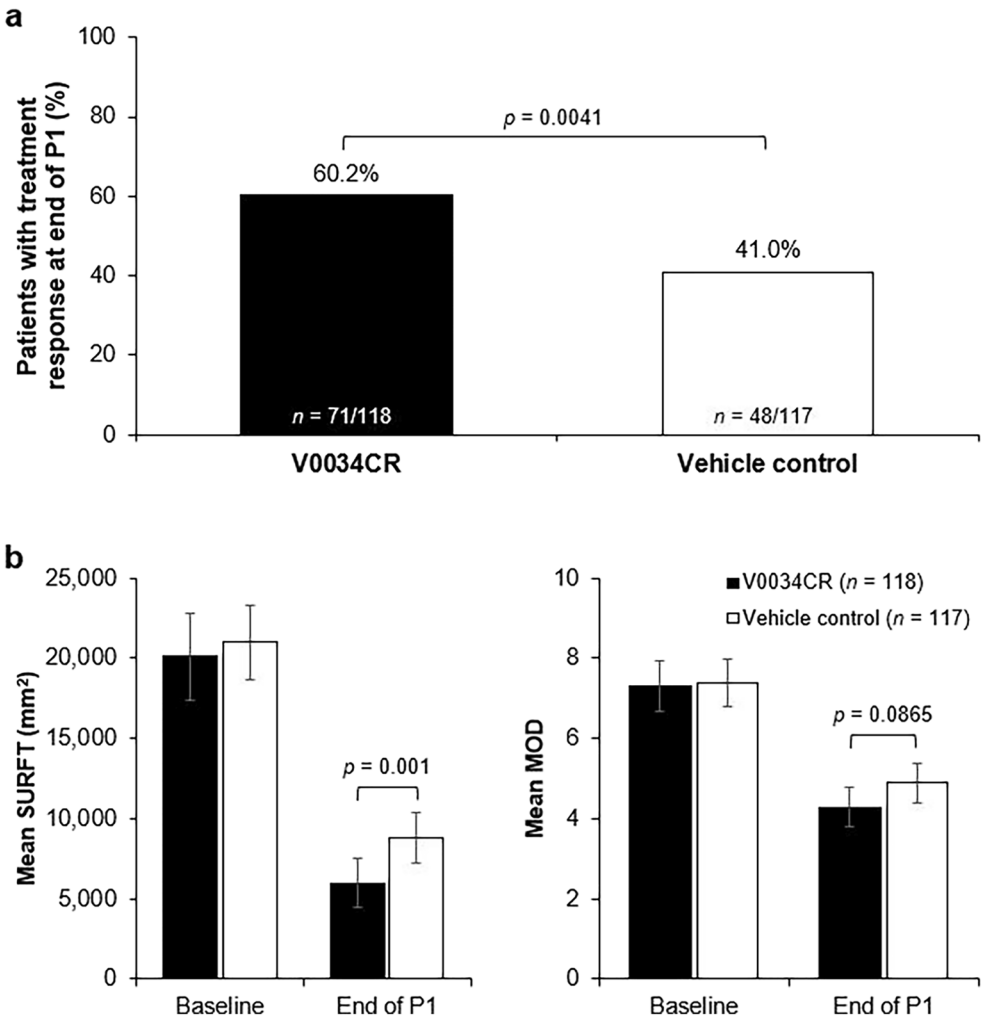

Fig. 3 Proportion of patients with treatment response (**a**) and instrumental measures of scaling (**b**) at the end of period I. In **a**, treatment response was defined as a xerosis severity score < 2 on all test areas and a score reduction from baseline of ≥ 2 on at least one test area; *p* value was based on Fisher's exact test. In **b**, error bars represent standard error the mean; *p* values were based on Wilcoxon signed-rank tests or Student's *t* tests. *MOD* mean optical density of squames, *P* period, *SURFT* total surface area of squames

through to the end of period III (10.4 ± 1.9 vs 7.5 ± 1.4 mm).

Patient acceptability of V0034CR was judged to be very high. At study end, 92.2% of patients in both groups rated the efficacy of V0034CR as satisfactory or very satisfactory, 92.7% rated ease of use as satisfactory or very satisfactory, and 92.7% rated the local tolerance of V0034CR as good or very good.

In the ITT population, there were no significant changes from baseline in SF-12 at the end of period I or period II in either group and no significant differences in SF-12 scores between the V0034CR group and control group at any time point (Table 3). In contrast, there were significant improvements in components of the SF-12 in the per-protocol population: the Mental Component Summary had improved significantly versus baseline at the end of period I in the vehicle group, and both the Physical and Mental Component Summary improved significantly versus baseline at the end of period I and remained improved at the end of period II in the V0034CR group. DLQI

Table 2 Time to relapse during period II (intent-to-treat population)

n (%)	V0034CR (*n* = 83)	Vehicle control (*n* = 61)
Relapse at day 35	18 (21.7)	18 (29.5)
Relapse at day 42	12 (14.5)	11 (18.0)
Relapse at day 49	17 (20.5)	12 (19.7)
No relapse at day 49	36 (43.4)	20 (32.8)

Analyses included patients with no persisting lesions (xerosis severity score < 2 on all test areas) at the end of period I. Relapse was defined as the recurrence of xerosis severity score ≥ 2 on at least one test area during period II

scores showed a significant reduction (indicating an improvement in QoL) versus baseline at the end of period I and II in both groups, and this was seen in both the ITT and per-protocol populations (Table 3). There was no significant between-group difference in SF-12 or DLQI scores at any time point.

Compliance

In the V0034CR group, the mean ± SEM number of product applications was 25.3 ± 0.6 during period I (28 days) and 79.2 ± 2.2 during period III (≥ 84 days), indicating good compliance. Similarly, the mean ± SEM amount of product applied in the V0034CR group was 11.9 ± 0.8 and 15.2 ± 1.3 g per application during period I and period III, respectively (compared with an estimated 20 g per application required for coverage of total xerotic area).

Tolerability of V0034CR

In total, 12 AEs related to V0034CR or vehicle control were reported in 12 patients (5.1%). All of these events were local, and included five patients (2.1%) with irritation or erythema at the application site (two patients in the V0034CR group and three in the vehicle control group), three patients (1.3%; all in the V0034CR group) with exacerbated pruritus, two patients (0.9%) with vesicles at the application site (one patient in the V0034CR group and one patient in the vehicle control group), one patient (0.4%; in the V0034CR group) with allergic dermatitis, and one patient (0.4%; in the V0034CR group) with dyshidrosis. No serious treatment-related AEs were reported; all treatment-related AEs except one (severe pruritus in the V0034CR group) were mild or moderate in severity, and seven led to premature study withdrawal. All 12 treatment-related AEs resolved without sequelae by discontinuing treatment temporarily or permanently.

DISCUSSION

This phase 3 study demonstrated the longer-term efficacy, acceptability, and tolerability of V0034CR emollient in patients with moderate-to-severe uremic xerosis. Once-daily application of V0034CR for 28 days was associated with greater rates of treatment response (based on investigator-assessed xerosis severity) compared with vehicle control, and coincided with objective improvements in the surface area and thickness of scaling. Improvements in xerosis severity were partially maintained without treatment in period II, but were fully recovered and then maintained with open-label V0034CR treatment during period III. V0034CR and vehicle control improved CKD-aP by a comparable magnitude during period I, while V0034CR demonstrated high patient acceptability and was well tolerated throughout. Together, these data suggest that the combination of glycerol and paraffin in V0034CR emollient may be an effective topical treatment option for patients with moderate-to-severe uremic xerosis and CKD-aP.

A previous study of V0034CR in patients with moderate-to-severe uremic xerosis found that treatment response (based on xerosis severity) was achieved in 73% of patients after twice-daily application for 7 days [26]. In comparison, once-daily V0034CR treatment for 28 days was associated with a treatment response rate of 60% in the present study, suggesting that good rates of xerosis improvement are achievable with less-frequent—and thus more convenient—dosing over an extended period. When treatment was discontinued during period II, a mild

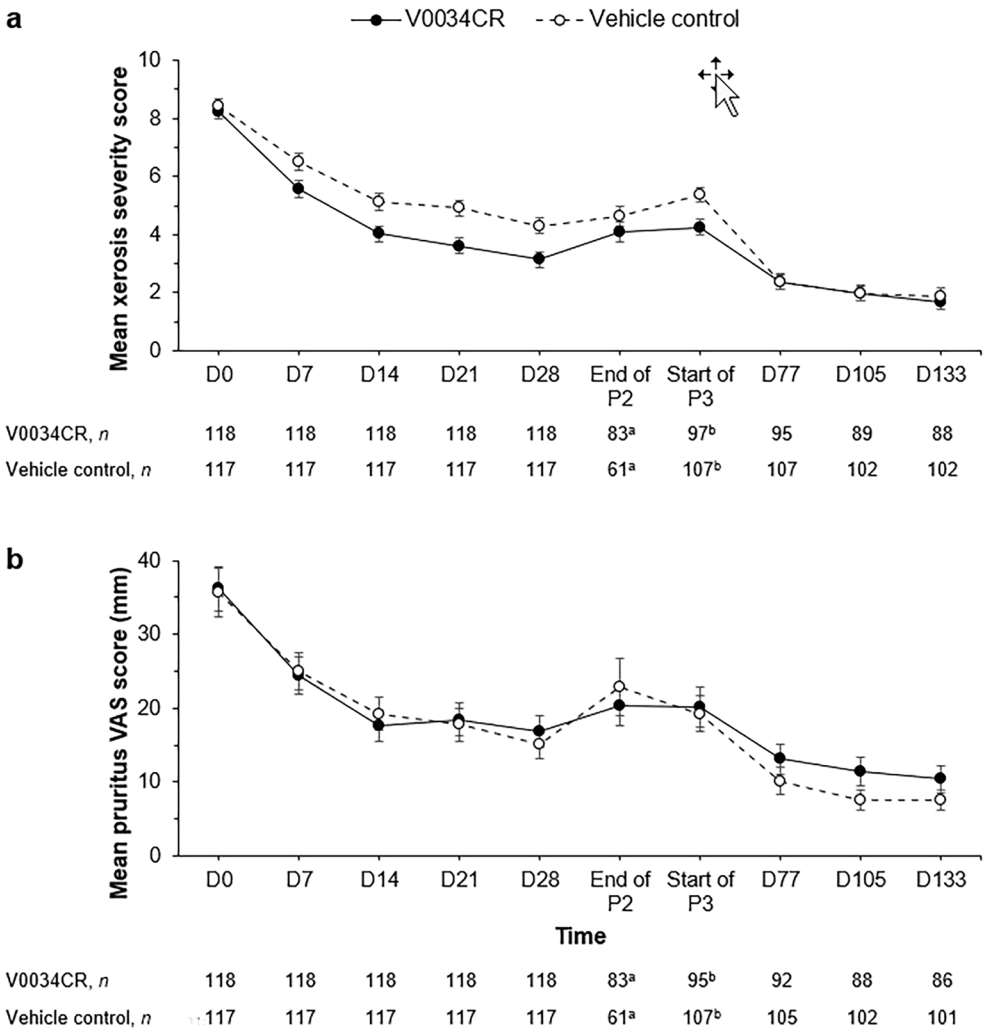

Fig. 4 Mean total xerosis severity scores (**a**) and pruritus VAS scores (**b**) over time. Analyses included in the intent-to-treat population; error bars represent standard error of the mean. [a]End of period II (P2) occurred on days 35 or 42 in patients who had relapsing lesions during period II, or day 49 in those with no persisting or relapsing lesions beforehand. [b]Start of period III (P3) occurred on day 28 in patients with persisting lesions at the end of period I, days 35 or 42 in patients who had relapsing lesions during period II, or day 49 in those with no persisting or relapsing lesions beforehand. *D* day, *P* period, *VAS* visual analog scale

residual effect of V0034CR on xerosis severity was observed, though not significantly different than that seen with vehicle control. This suggests that glycerol and paraffin have mainly a palliative effect on restoring skin hydration and barrier function, and highlights the importance of continuous therapy even when lesions remit. The course of uremic xerosis severity over time revealed the rapid benefits of V0034CR treatment during period I, which were maintained with ongoing treatment during period III. The durability of the V0034CR treatment effect was also very good, with a low rate of recurrence among those with remitting lesions who continued V0034CR maintenance therapy during period III (2%).

The efficacy of V0034CR on CKD-aP was also assessed. Although CKD-aP severity was greatly reduced over the course of the study, no statistical difference was observed between groups

Table 3 Quality of life assessments

Mean ± SEM score	Vehicle			V0034CR		
	Baseline	End period I	End period II	Baseline	End period I	End period II
ITT population	(*n* = 117)	(*n* = 117)	(*n* = 61)	(*n* = 118)	(*n* = 118)	(*n* = 83)
SF-12						
PCS	37.0 (1.1)	37.1 (0.9)	36.3 (1.6)	37.6 (1.2)	38.3 (1.1)	35.9 (1.5)
MCS	46.9 (1.2)	47.0 (1.1)	44.9 (1.5)	48.4 (1.3)	49.3 (1.1)	45.3 (1.6)
DLQI	4.8 (0.4)	2.5 (0.3)[a]	3.2 (0.6)[a]	4.9 (0.4)	2.6 (0.3)[a]	4.4 (0.8)[a]
PP population	(*n* = 96)	(*n* = 87)	(*n* = 57)	(*n* = 87)	(*n* = 83)	(*n* = 69)
SF-12						
PCS	35.8 (1.1)	37.6 (1.1)	38.0 (1.5)	35.0 (1.1)	37.5 (1.3)[b]	39.1 (1.4)[b]
MCS	44.5 (1.2)	47.2 (1.1)[b]	46.8 (1.2)[b]	45.2 (1.3)	49.5 (1.1)[a]	49.1 (1.3)[b]
DLQI	5.1 (0.5)	2.3 (0.3)[a]	2.6 (0.4)[a]	4.9 (0.5)	2.2 (0.3)[a]	2.2 (0.4)[a]

DLQI Dermatology Life Quality Index, *ITT* intent-to-treat, *MCS* Mental Component Summary, *PCS* Physical Component Summary, *PP* per-protocol, *SEM* standard error of the mean, *SF-12* Short Form-12

[a] $p < 0.001$ vs baseline

[b] $p < 0.01$ vs baseline

treated with V0034CR and its vehicle control. Several studies have demonstrated a positive correlation between uremic xerosis and CKD-aP [2, 3, 9, 10, 12]; therefore, we expected that glycerol and paraffin in V0034CR would reduce pruritus beyond vehicle control via their effects on xerosis. However, no additional antipruritic benefit of glycerol and paraffin was shown, suggesting that the main antipruritic effect of V0034CR may be exerted by ingredient(s) in its oil-in-water emulsion base. The fact that significant improvements in DLQI scores were seen in both groups suggests that relief of pruritus is an important determinant of QoL in patients with uremic xerosis.

The tolerability profile of V0034CR after long-term use was very good. Its topical route of administration did not result in any systemic AEs, and local AEs were infrequent (irritation or erythema in 2.1% of patients, exacerbated pruritus in 1.3%, application site vesicles in 0.9%, allergic dermatitis in 0.4%, and dyshidrosis in 0.4%). In the context of this study population, who are particularly prone to developing irritation to external agents, these results may be considered as excellent. Patient acceptability of V0034CR based on its efficacy, ease of use, and local tolerance was also very high. Furthermore, good treatment compliance was demonstrated by the patients, who on average used 12–15 g of V0034CR per application, once per day, during both the initial and maintenance therapy periods.

We are aware that there are some limitations of our study. The study was conducted on a limited number of patients from a small sample of clinical sites across Europe, which may affect the generalizability of our findings. Although xerosis was assessed using El Gammal's severity score [27] and D-Squame measures of scaling [28], corneometry and evaporimetry outcomes would have provided additional data to understand the skin-hydrating and barrier-restoring effects of V0034CR in patients with uremic xerosis. In addition, the control in our study was the topical vehicle, so our research does not provide any data on the efficacy of V0034CR relative to other active treatments currently used for CKD-aP. Further research is warranted in more diverse

cohorts of patients, and comparing V0034CR with current standard of care.

CONCLUSION

Data from this phase 3 study support the notion that V0034CR, an emollient and skin protectant containing glycerol 15% and paraffin 10%, is an effective long-term treatment option for patients with moderate-to-severe uremic xerosis. Both active treatment and the vehicle ameliorated pruritus, suggesting that the oil-in-water emulsion has antipruritic effects in patients with CKD-aP.

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Data Availability. The datasets created and analyzed during this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of Interest. Jacek Szepietowski has served as a consultant and/or advisor for AbbVie, LEO Pharma, Novartis, Pfizer, Pierre Fabre, Sanofi-Genzyme, Trevi, UCB, and Vifor; a speaker for AbbVie, Almirall, Eli Lilly, Janssen-Cilag, LEO Pharma, Novartis, Pfizer, and Sanofi-Genzyme; and an investigator for AbbVie, Almirall, Amgen, AnaptysBio, BMS, Boehringer Ingelheim, Celtrion, Galapagos, Galderma, HELM AG, Incyte, InfraRx, Janssen-Cilag, Kiniksa, LEO Pharma, MedImmune, Menlo Therapeutics, Merck, Novartis, Pfizer, Pierre Fabre, Regeneron, Teva, Trevi, and UCB. Lajos Kemeny and Thomas Mettang have no conflicts of interest to declare. Petr Arenberger has served as a consultant and/or advisor for AbbVie, BMS, LEO Pharma, Novartis, Pfizer, Pierre Fabre, MSD, Sanofi, and UCB; and a speaker for AbbVie, Almirall, BMS, Johnson and Johnson, LEO Pharma, Novartis, MSD, and Pfizer.

Ethical Approval. This study was conducted in compliance with the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice Guidelines, and applicable local laws. The study protocol was approved in each country by applicable independent ethics committees and competent authorities (Supplementary Table S2), and written informed consent was obtained from all participants. This study is registered with ClinicalTrials.gov (NCT01084148) and the European Union Clinical Trials Register (EudraCT 2006-002201-31).

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